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PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * Welcome to STN International * * * * * * * * *

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now available on STN
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NEWS 8 Sep 16 Experimental properties added to the REGISTRY file
NEWS 9 Sep 16 CA Section Thesaurus available in CAPLUS and CA
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NEWS 18 Dec 17 Adis Clinical Trials Insight now available on STN
NEWS 19 Jan 29 Simultaneous left and right truncation added to COMPENDEX,
ENERGY, INSPEC
NEWS 20 Feb 13 CANCERLIT is no longer being updated
NEWS 21 Feb 24 METADEX enhancements
NEWS 22 Feb 24 PCTGEN now available on STN
NEWS 23 Feb 24 TEMA now available on STN
NEWS 24 Feb 26 NTIS now allows simultaneous left and right truncation
NEWS 25 Feb 26 PCTFULL now contains images
NEWS 26 Mar 04 SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27 Mar 20 EVENTLINE will be removed from STN
NEWS 28 Mar 24 PATDPAFULL now available on STN
NEWS 29 Mar 24 Additional information for trade-named substances without
structures available in REGISTRY
NEWS 30 Apr 11 Display formats in DGENE enhanced
NEWS 31 Apr 14 MEDLINE Reload
NEWS 32 Apr 17 Polymer searching in REGISTRY enhanced
NEWS 33 Jun 13 Indexing from 1947 to 1956 added to records in CA/CAPLUS
NEWS 34 Apr 21 New current-awareness alert (SDI) frequency in
WPIDS/WPINDEX/WPIX
NEWS 35 Apr 28 RDISCLOSURE now available on STN
NEWS 36 May 05 Pharmacokinetic information and systematic chemical names
added to PHAR
NEWS 37 May 15 MEDLINE file segment of TOXCENTER reloaded
NEWS 38 May 15 Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS 39 May 16 CHEMREACT will be removed from STN
NEWS 40 May 19 Simultaneous left and right truncation added to WSCA

NEWS 41 May 19 RAPRA enhanced with new search field, simultaneous left and right truncation
NEWS 42 Jun 06 Simultaneous left and right truncation added to CBNB
NEWS 43 Jun 06 PASCAL enhanced with additional data
NEWS 44 Jun 20 2003 edition of the FSTA Thesaurus is now available
NEWS 45 Jun 25 HSDB has been reloaded

NEWS EXPRESS April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003

NEWS HOURS STN Operating Hours Plus Help Desk Availability

NEWS INTER General Internet Information

NEWS LOGIN Welcome Banner and News Item

NEWS PHONE Direct Dial and Telecommunication Network Access to STN

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Enter NEWS followed by the item number or name to see news on that specific topic.

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FILE 'HOME' ENTERED AT 14:06:37 ON 01 JUL 2003

=> file req

COST IN U.S. DOLLARS

SINCE FILE TOTAL

ENTRY SESSION

FULL ESTIMATED COST 0.21

FILE 'REGISTRY' ENTERED AT 14:06:42 ON 01 JUL 2003
PAGE 25 OF 25 PAGES

Property values tagged with IC are from the ZIC/VINITI data file

STRUCTURE FILE UPDATES: 30 JUN 2003 HIGHEST RN 540462-79-1
DICTIONARY FILE UPDATES: 30 JUN 2003 HIGHEST RN 540462-79-1

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

≡> S 220488-46-OP/RN

L1 0 220488-46-OP/RN

=> d 11

L1 HAS NO ANSWERS

L1 0 SEA FILE=REGISTRY PLU=ON 220488-46-OP/RN

=> s 11

L2 0 220488-46-OP/RN

=> d 220488-46-OP/RN

'220488-46-OP' MUST END IN '/Q', '/A', '/L', '/S' OR '/B'

The saved name for a query (or structure or screen set) must end with '/Q'. The saved name for an answer set must end with '/A'. The saved name for an L# list must end with '/L'. SDI request names must end with '/S'. To see a list of all saved query, answer set,, and L# list names for this loginid, enter "DISPLAY SAVED" at an arrow prompt (=>). Enter "DISPLAY SAVED/S" to see a list of SDI request names. Enter "DISPLAY SAVED/B" to see a list of BATCH search requests.

=> d 220488-46-OP/RN/Q

'220488-46-OP' MUST END IN '/Q', '/A', '/L', '/S' OR '/B'

The saved name for a query (or structure or screen set) must end with '/Q'. The saved name for an answer set must end with '/A'. The saved name for an L# list must end with '/L'. SDI request names must end with '/S'. To see a list of all saved query, answer set,, and L# list names for this loginid, enter "DISPLAY SAVED" at an arrow prompt (=>). Enter "DISPLAY SAVED/S" to see a list of SDI request names. Enter "DISPLAY SAVED/B" to see a list of BATCH search requests.

=> file caplus

COST IN U.S. DOLLARS

SINCE FILE ENTRY	TOTAL SESSION
2.40	2.61

FULL ESTIMATED COST

FILE 'CAPLUS' ENTERED AT 14:10:21 ON 01 JUL 2003
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FILE COVERS 1907 - 1 Jul 2003 VOL 139 ISS 1
 FILE LAST UPDATED: 30 Jun 2003 (20030630/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 130:168387?DN
 '?' TRUNCATION SYMBOL NOT VALID WITHIN '168387?DN'
 The truncation symbol ? may be used only at the end of a search term. To specify a variable character within a word use '!', e.g., 'wom!n' to search for both 'woman' and 'women'. Enter "HELP TRUNCATION" at an arrow prompt (>) for more information.

=> s 130:168387/DN
 L3 1 130:168387/DN

=> d 13 fbib hitstr abs total

L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
 AN 1999:113656 CAPLUS
 DN 130:168387
 TI Irreversible inhibitors of tyrosine kinases
 IN Bridges, Alexander James
 PA Warner-Lambert Company, USA
 SO PCT Int. Appl., 124 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9906378	A1	19990211	WO 1998-US15784	19980729
	W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			US 1997-54060P P	19970729
	AU 9887607	A1	19990222	AU 1998-87607	19980729
				US 1997-54060P P	19970729
				WO 1998-US15784W	19980729
	US 6127374	A	20001003	US 1999-269545	19990325
				US 1997-54060P P	19970729
				WO 1998-US15784W	19980729
	US 6562818	B1	20030513	US 2000-593031	20000613
				US 1997-54060P P	19970729
				WO 1998-US15784W	19980729
				US 1999-269545 A319990325	

OS MARPAT 130:168387
 AB Pyrimidine derivs. that are irreversible inhibitors of tyrosine kinases are reported. Thus, PhCH₂OH was treated with 4-FC₆H₄NO₂ to give 4-PhCH₂C₆H₄NO₂, which was reduced to the amine and used to aminate 4-chloro-6-nitroquinazoline hydrochloride. The resulting 6-nitro-4-(4-benzyloxyanilino)quinazoline hydrochloride was reduced to the amine and acylated to give N-[4-(4-benzyloxyanilino)quinazolin-6-yl]acrylamide (I). I had an IC₅₀ for inhibition of epidermal growth factor receptor tyrosine kinase of 3.6 nM.

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

10016280.5

Page 5

```
=> log y
COST IN U.S. DOLLARS          SINCE FILE      TOTAL
                                ENTRY           SESSION
FULL ESTIMATED COST          6.22            8.83
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) SINCE FILE      TOTAL
CA SUBSCRIBER PRICE           -0.65           -0.65
```

STN INTERNATIONAL LOGOFF AT 14:13:38 ON 01 JUL 2003

L4 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2003 ACS
 AN 1994:217715 CAPLUS
 DN 120:217715
 TI Quinazoline tyrosine kinase-inhibiting anticancer agents
 IN Barker, Andrew J.
 PA Zeneca Ltd., UK
 SO Can. Pat. Appl., 99 pp.
 CODEN: CPXXEB
 DT Patent
 LA English
 FAN CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CA 2086968	AA	19930721	CA 1993-2086968	19930108
	CA 2086968	C	19980623	GB 1992-1095	A 19920120
			GB 1992-13572	A 19920626	
			GB 1992-23735	A 19921112	
	ZA 9300015	A	19930720	ZA 1993-15	19930104
	AU 9331010	A1	19930722	GB 1992-1095	A 19920120
	AU 661533	B2	19950727	AU 1993-31010	19930104
	HU 63153	A2	19930728	GB 1992-1095	A 19920120
			GB 1992-13572	A 19920626	
			GB 1992-23735	A 19921112	
			HU 1993-94	19930115	
			GB 1992-1095	A 19920120	
			GB 1992-13572	A 19920626	

<7/1/2003>

Patel

Welcome to STN International! Enter x:x

LOGINID:ssspta1611sxp

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * Welcome to STN International * * * * * * * * *

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NEWS 23 Feb 24 TEMA now available on STN
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structures available in REGISTRY
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NEWS 31 Apr 14 MEDLINE Reload
NEWS 32 Apr 17 Polymer searching in REGISTRY enhanced
NEWS 33 Jun 13 Indexing from 1947 to 1956 added to records in CA/CAPLUS
NEWS 34 Apr 21 New current-awareness alert (SDI) frequency in
WPIDS/WPINDEX/WPIX
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added to PHAR
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NEWS 39 May 16 CHEMREACT will be removed from STN
NEWS 40 May 19 Simultaneous left and right truncation added to WSCA

NEWS 41 May 19 RAPRA enhanced with new search field, simultaneous left and right truncation
NEWS 42 Jun 06 Simultaneous left and right truncation added to CBNB
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NEWS EXPRESS	April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
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NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

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STRUCTURE FILE UPDATES: 30 JUN 2003 HIGHEST RN 540462-79-1
DICTIONARY FILE UPDATES: 30 JUN 2003 HIGHEST RN 540462-79-1

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

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Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

三

Uploading 10016280.5

L1 STRUCTURE UPLOADED

=> d 11
L1 HAS NO ANSWERS
L1 STR
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

Structure attributes must be viewed using STN Express query preparation.

=> s 11
SAMPLE SEARCH INITIATED 14:39:14 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 302 TO ITERATE

100.0% PROCESSED 302 ITERATIONS 7 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 4998 TO 7082
PROJECTED ANSWERS: 7 TO 298

L2 7 SEA SSS SAM L1

=> s 11 sss full
FULL SEARCH INITIATED 14:39:21 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 6071 TO ITERATE

100.0% PROCESSED 6071 ITERATIONS 82 ANSWERS
SEARCH TIME: 00.00.01

L3 82 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS SINCE FILE TOTAL
FULL ESTIMATED COST ENTRY SESSION
148.15 148.36

FILE 'CAPLUS' ENTERED AT 14:39:27 ON 01 JUL 2003
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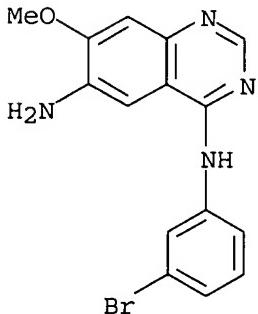
FILE COVERS 1907 - 1 Jul 2003 VOL 139 ISS 1
FILE LAST UPDATED: 30 Jun 2003 (20030630/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> S 13
L4 24 L3

=> D 14 fbib hitstr abs total

L4 ANSWER 1 OF 24 CAPLUS COPYRIGHT 2003 ACS
 AN 2002:951575 CAPLUS
 DN 138:117246
 TI Mapping the Binding Site of a Large Set of Quinazoline Type EGF-R Inhibitors Using Molecular Field Analyses and Molecular Docking Studies
 AU Hou, Tingjun; Zhu, Lili; Chen, Lirong; Xu, Xiaojie
 CS College of Chemistry and Molecular Engineering, Peking University, Beijing, 100871, Peop. Rep. China
 SO Journal of Chemical Information and Computer Sciences (2003), 43(1), 273-287
 CODEN: JCISD8; ISSN: 0095-2338
 PB American Chemical Society
 DT Journal
 LA English
 IT 171745-06-5
 RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
 (QSAR (quant. structure-activity relationship) studies on quinazoline type epidermal growth factor receptors (EGF-R) inhibitors using mol. field analyses and mol. docking studies)
 RN 171745-06-5 CAPLUS
 CN 4,6-Quinazolinediamine, N4-(3-bromophenyl)-7-methoxy- (9CI) (CA INDEX NAME)



AB In the current work, three-dimensional QSAR studies for one large set of quinazoline type epidermal growth factor receptor (EGF-R) inhibitors were conducted using two types of mol. field anal. techniques: comparative mol. field anal. (CoMFA) and comparative mol. similarity indexes anal. (CoMSIA). These compds. belonging to six different structural classes were randomly divided into a training set of 122 compds. and a test set of 13 compds. The statistical results showed that the 3D-QSAR models derived from CoMFA were superior to those generated from CoMSIA. The most optimal CoMFA model after region focusing bears significant cross-validated r^2_{cv} of 0.60 and conventional r^2 of 0.92. The predictive power of the best

CoMFA model was further validated by the accurate estn. to these compds. in the external test set, and the mean agreement of exptl. and predicted log(IC50) values of the inhibitors is 0.6 log unit. Sep. CoMFA models were conducted to evaluate the influence of different partial charges (Gasteiger-Marsili, Gasteiger-Huckel, MMFF94, ESP-AM1, and MPA-AM1) on the statistical quality of the models. The resulting CoMFA field map provides information on the geometry of the binding site cavity and the relative wts. of various properties in different site pockets for each of the substrates considered. Moreover, in the current work, we applied MD simulations combined with MM/PBSA (Mol. mechanics/Possion-Boltzmann Surface Area) to det. the correct binding mode of the best inhibitor for which no ligand-protein crystal structure was present. To proceed, we define the following procedure: three hundred picosecond mol. dynamics simulations were first performed for the four binding modes suggested by DOCK 4.0 and manual docking, and then MM/PBSA was carried out for the collected snapshots. The most favorable binding mode identified by MM/PBSA has a binding free energy about 10 kcal/mol more favorable than the second best one. The most favorable binding mode identified by MM/PBSA can give satisfactory explanation of the SAR data of the studied mols. and is in good agreement with the contour maps of CoMFA. The most favorable binding mode suggests that with the quinazoline-based inhibitor, the N3 atom is hydrogen-bonded to a water mol. which, in turn, interacts with Thr 766, not Thr 830 as proposed by Wissner et al. (J. Med. Chem. 2000, 43, 3244). The predicted complex structure of quinazoline type inhibitor with EGF-R as well as the pharmacophore mapping from CoMFA can interpret the structure activities of the inhibitors well and afford us important information for structure-based drug design.

RE.CNT 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 24 CAPLUS COPYRIGHT 2003 ACS
 AN 2002:487536 CAPLUS
 DN 137:63250
 TI Quinazoline derivatives as inhibitors of human EFG tyrosine kinase
 IN Himmelsbach, Frank; Langkopf, Elke; Blech, Stefan; Jung, Birgit; Baum,
 Elke; Solca, Flavio
 PA Boehringer Ingelheim Pharma Kg, Germany
 SO PCT Int. Appl., 64 pp.
 CODEN: PIXXD2
 DT Patent
 LA German
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002050043	A1	20020627	WO 2001-EP14569	20011212
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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 DE 2000-10063435A 20001220
 US 2000-259201PP 20001228

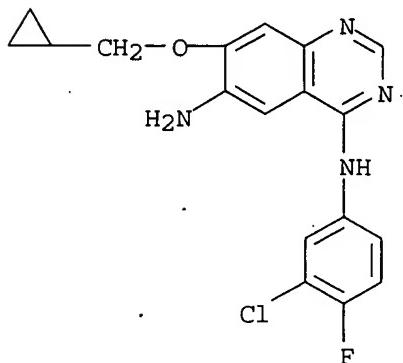
OS MARPAT 137:63250

IT 290304-07-3

RL: RCT (Reactant); RACT (Reactant or reagent)
 (prepn. of quinazoline derivs. as inhibitors of human EFG tyrosine kinase)

RN 290304-07-3 CAPLUS

CN 4,6-Quinazolinediamine, N4-(3-chloro-4-fluorophenyl)-7-(cyclopropylmethoxy) - (9CI) (CA INDEX NAME)

IT 314771-75-0P 314771-76-1P 314771-77-2P
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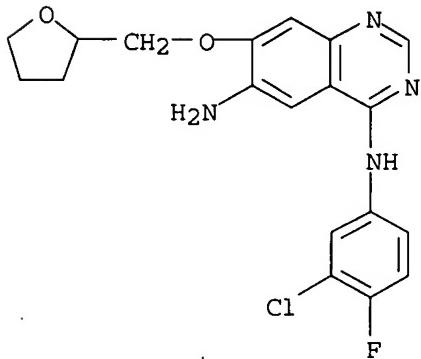
439081-58-0P 439081-59-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of quinazoline derivs. as inhibitors of human EFG tyrosine kinase)

RN 314771-75-0 CAPLUS

CN 4,6-Quinazolinediamine, N4-(3-chloro-4-fluorophenyl)-7-[(tetrahydro-2-furanyl)methoxy] - (9CI) (CA INDEX NAME)

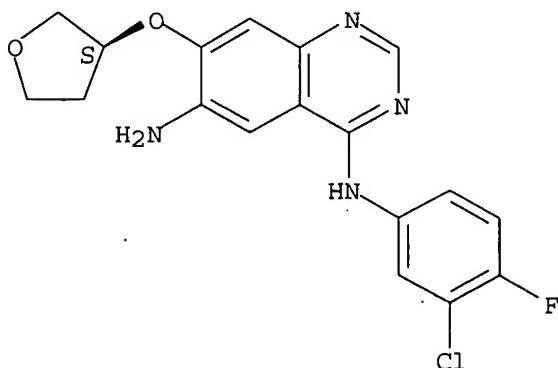


RN 314771-76-1 CAPLUS

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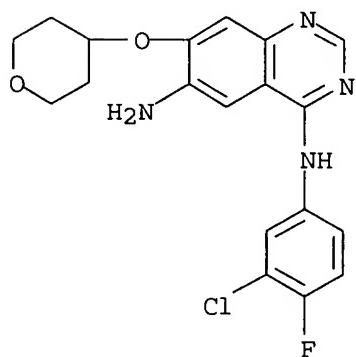
furanyl]oxy] - (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 314771-77-2 CAPLUS

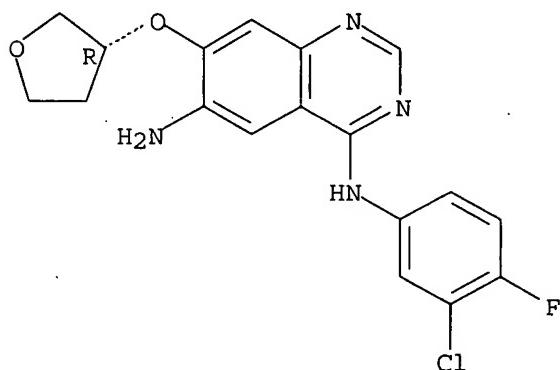
CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-[(tetrahydro-2H-pyran-4-yl)oxy]- (9CI) (CA INDEX NAME)



RN 402855-03-2 CAPLUS

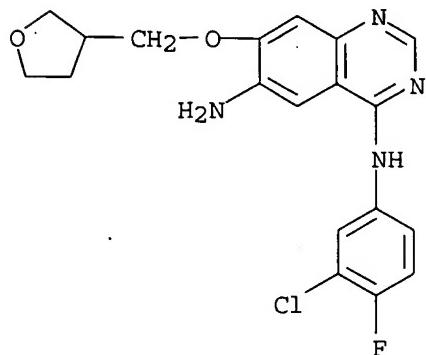
CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-[[(3R)-tetrahydro-3-furanyl]oxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



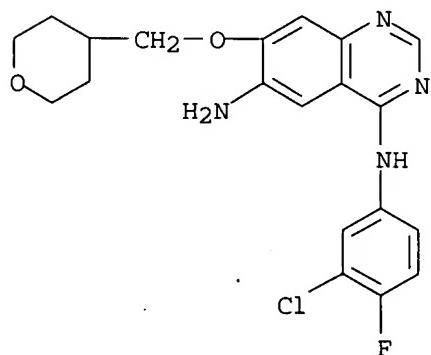
RN 402855-04-3 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-[(tetrahydro-3-furanyl)methoxy]- (9CI) (CA INDEX NAME)



RN 402855-05-4 CAPLUS

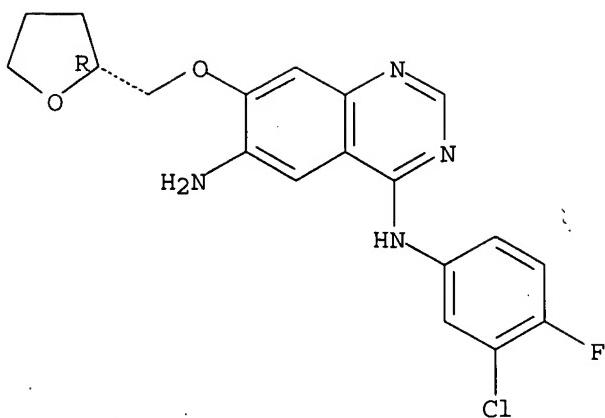
CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-[(tetrahydro-2H-pyran-4-yl)methoxy]- (9CI) (CA INDEX NAME)



RN 439081-58-0 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-[[(2R)-tetrahydro-2-furanyl]methoxy]- (9CI) (CA INDEX NAME)

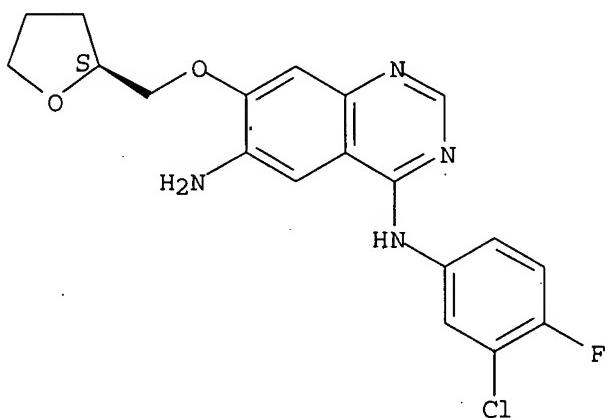
Absolute stereochemistry.



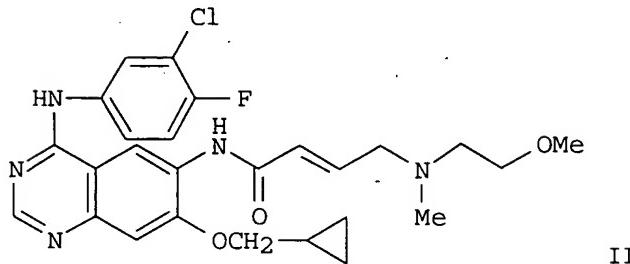
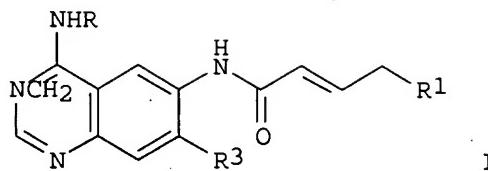
RN 439081-59-1 CAPLUS

CN 4,6-Quinazolinediamine, N4- (3-chloro-4-fluorophenyl)-7- [(2S)-tetrahydro-2-furanyl]methoxy] - (9CI) (CA INDEX NAME)

Absolute stereochemistry.



GI



AB Quinazoline derivs. I [R = PhCH₂, PhCHMe, 3,4-Cl(F)C₆H₃; R1 = NMe₂, NEt₂, NET₂CH₂CH₂OMe, N(CH₂CH₂OMe)₂, morpholino; R2 = Me, Et, CHMe₂, cyclopropyl, CH₂CH₂OMe, 3-tetrahydrofuryl, 2-tetrahydrofurylmethyl, 3-tetrahydrofurylmethyl, 4-tetrahydropyranyl, 4-tetrahydropyranylmethyl; R3 = cyclopropylmethoxy, cyclobutyloxy, cyclopentyloxy, 3-tetrahydrofuranyloxy, 2-tetrahydrofuranylmethoxy, 3-tetrahydrofuranylmethoxy, 4-tetrahydropyranylmethoxy, 4-tetrahydropyranylmethoxy] were prep'd. for use as inhibitors of signal transduction caused by human EFG receptor tyrosine kinase. They are useful in the treatment of tumoral diseases, diseases of the lung and the respiratory tract, the gastrointestinal tract, and the gallbladder and bile ducts. Thus, the quinazoline II was prep'd. by converting bromocrotonic acid to its chloride, and reaction with 4-[(3-chloro-4-fluorophenyl)amino]-6-amino-7-cyclopropylmethoxyquinazoline, followed by MeNHCH₂CH₂OMe. II had an IC₅₀ against human EFG receptor kinase of 0.7 nM.

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 24 CAPLUS COPYRIGHT 2003 ACS
 AN 2002:171892 CAPLUS
 DN 136:216762
 TI Preparation of 4-amino-6-heterocyclcarbonylaminoquinazolines as epidermal growth factor receptor signal transduction inhibitors
 IN Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
 PA Boehringer Ingelheim Pharma Kg, Germany
 SO PCT Int. Appl., 53 pp.
 CODEN: PIXXD2

DT Patent
 LA German
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002018376	A1	20020307	WO 2001-EP9536	20010818
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,			

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,
 PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
 US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
 BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 2000-10042062A 20000826
 DE 10042062 A1 20020307 DE 2000-10042062 20000826
 AU 2001095482 A5 20020313 AU 2001-95482 20010818
 DE 2000-10042062A 20000826
 WO 2001-EP9536 W 20010818
 EP 1315720 A1 20030604 EP 2001-976108 20010818
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 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
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 WO 2001-EP9536 W 20010818
 US 2002115675 A1 20020822 US 2001-934631 20010822
 DE 2000-10042062A 20000826
 US 2000-230542PP 20000905

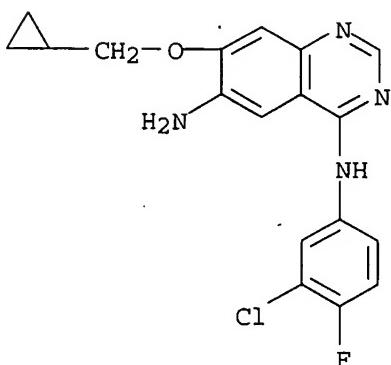
OS MARPAT 136:216762

IT 290304-07-3P

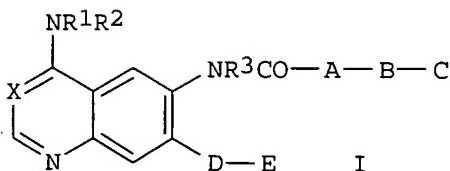
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)
 (prep. of (amino)(heterocyclylcarbonylamino)quinazolines as epidermal
 growth factor receptor signal transduction inhibitors)

RN 290304-07-3 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-
 (cyclopropylmethoxy)- (9CI) (CA INDEX NAME)



GI



AB Title compds. [I; X = N, (substituted) methynyl; R1 = H, Me; R2 =

(substituted) Ph, PhCH₂, 1-phenylethyl; R₃ = H, Me; A = (substituted) vinyl, ethynyl, 1,3-butadien-1,4-yl; B = (substituted) alkenyl, alkenylcarbonyl, etc.; C = (substituted) 2-oxomorpholin-4-yl, etc; D = oxyalkenyl, O; E = (substituted) amino, alkenylimino, imidazolyl, cycloalkyl; or DE = H, (substituted) alkoxy, etc.], were prep'd. Thus, 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-[N-(ethoxycarbonylmethyl)-N-((R)-2-hydroxy-3-methoxypropyl)amino]-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline (prepn. given) and MeSO₂OH in MeCN were stirred for 4 h under reflux to give 69% 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-[(R)-2-methoxymethyl-6-oxomorpholin-4-yl]-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline. The latter inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERC cells with IC₅₀ = 2 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 24 CAPLUS COPYRIGHT 2003 ACS
AN 2002:171891 CAPLUS
DN 136:216761
TI Preparation of 4-amino-6-vinylcarbonylaminoquinazolines as epidermal growth factor receptor signal transduction inhibitors
IN Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PA Boehringer Ingelheim Pharma Kg, Germany
SO PCT Int. Appl., 52 pp.
CODEN: PIXXD2

DT Patent
LA German
FAN.CNT 1

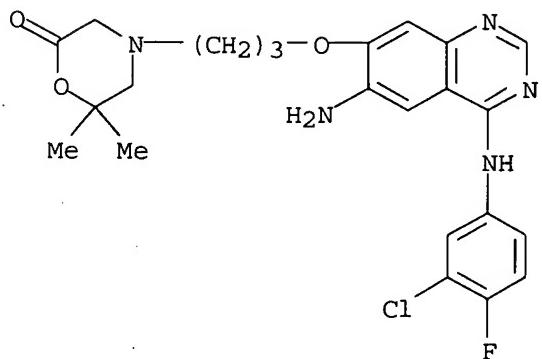
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002018375	A1	20020307	WO 2001-EP9534	20010818
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DE	10042064	A1	20020307	DE 2000-10042064	20000826
AU	2002010444	A5	20020313	AU 2002-10444	20010818
				DE 2000-10042064A	20000826
				WO 2001-EP9534 W	20010818
US	6403580	B1	20020611	US 2001-935498	20010823
				DE 2000-10042064A	20000826
				US 2000-230541PP	20000905

OS MARPAT 136:216761
IT 402723-54-0P 402723-56-2P 402723-58-4P
402723-60-8P 402723-61-9P 402723-62-0P
402723-63-1P 402723-64-2P 402723-94-8P
402723-95-9P 402723-96-0P 402723-97-1P
402723-98-2P 402723-99-3P 402724-00-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of (amino)(vinylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)

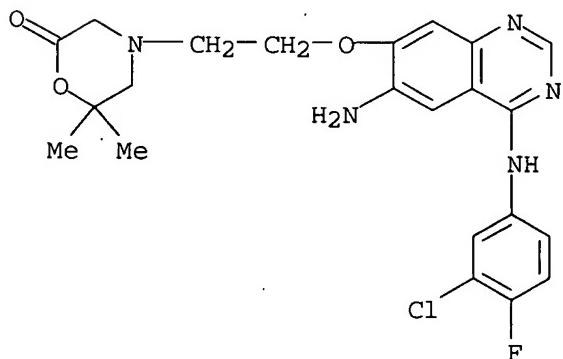
RN 402723-54-0 CAPLUS

CN 2-Morpholinone, 4-[3-[(6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl]oxy]propyl]-6,6-dimethyl- (9CI) (CA INDEX NAME)



RN 402723-56-2 CAPLUS

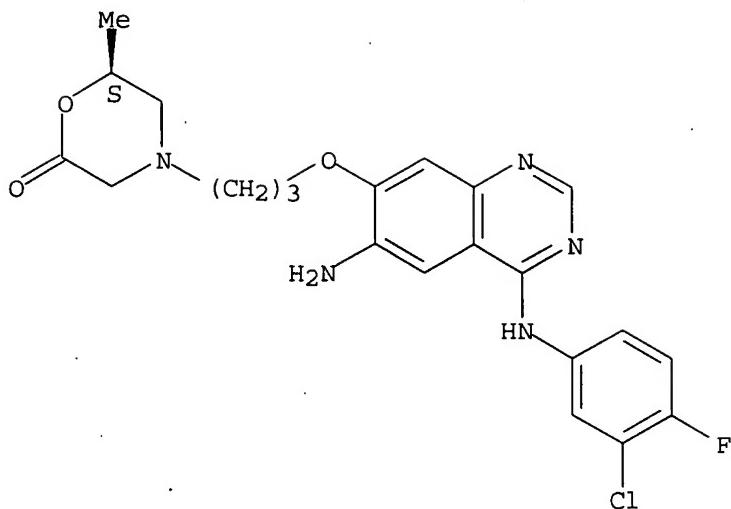
CN 2-Morpholinone, 4-[2-[(6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl]oxy]ethyl]-6,6-dimethyl- (9CI) (CA INDEX NAME)



RN 402723-58-4 CAPLUS

CN 2-Morpholinone, 4-[3-[(6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl]oxy]propyl]-6-methyl-, (6S)- (9CI) (CA INDEX NAME)

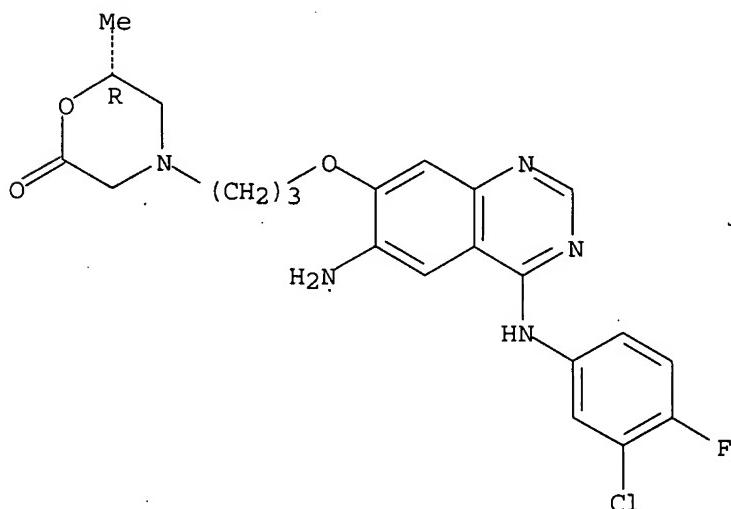
Absolute stereochemistry.



RN 402723-60-8 CAPLUS

CN 2-Morpholinone, 4-[3-[(6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl)oxy]propyl]-6-methyl-, (6R)- (9CI) (CA INDEX NAME)

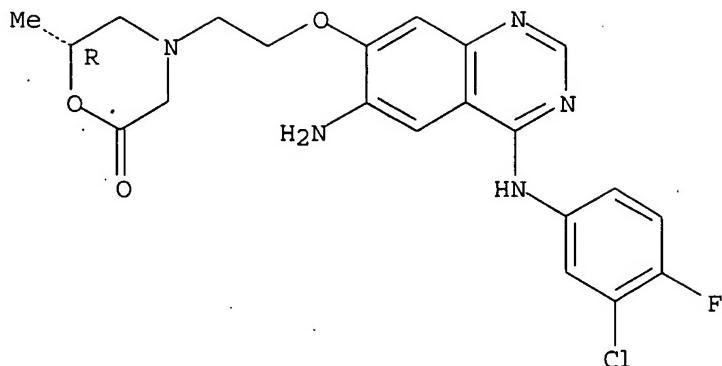
Absolute stereochemistry.



RN 402723-61-9 CAPLUS

CN 2-Morpholinone, 4-[2-[(6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl)oxy]ethyl]-6-methyl-, (6R)- (9CI) (CA INDEX NAME)

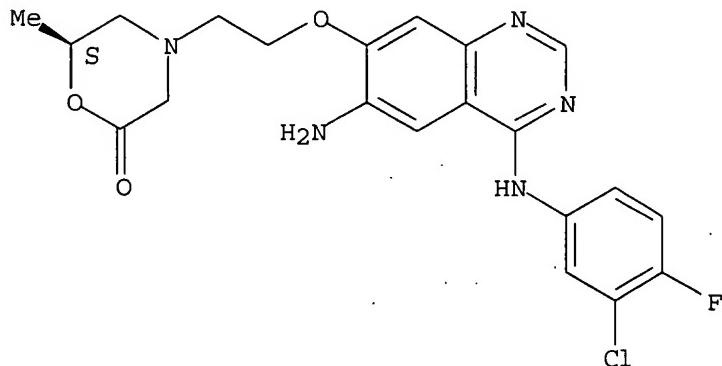
Absolute stereochemistry.



RN 402723-62-0 CAPLUS

CN 2-Morpholinone, 4-[2-[[6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl]oxy]ethyl]-6-methyl-, (6S)- (9CI) (CA INDEX NAME)

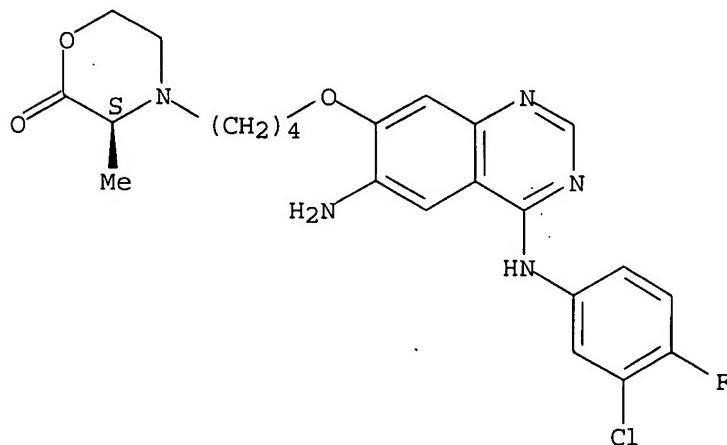
Absolute stereochemistry.

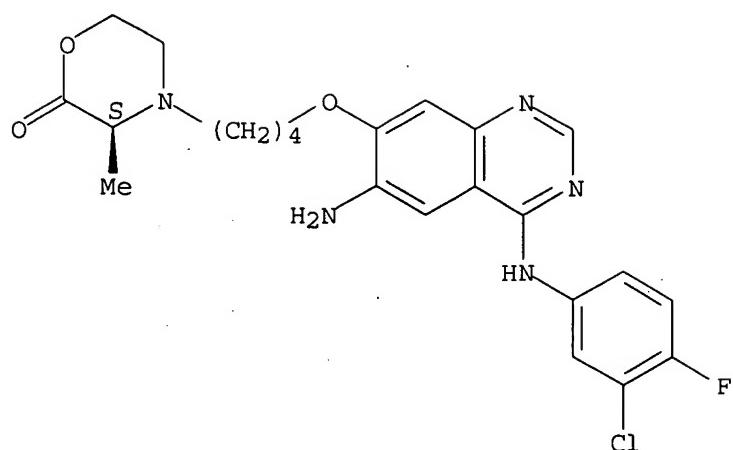


RN 402723-63-1 CAPLUS

CN 2-Morpholinone, 4-[4-[[6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl]oxy]butyl]-3-methyl-, (3S)- (9CI) (CA INDEX NAME)

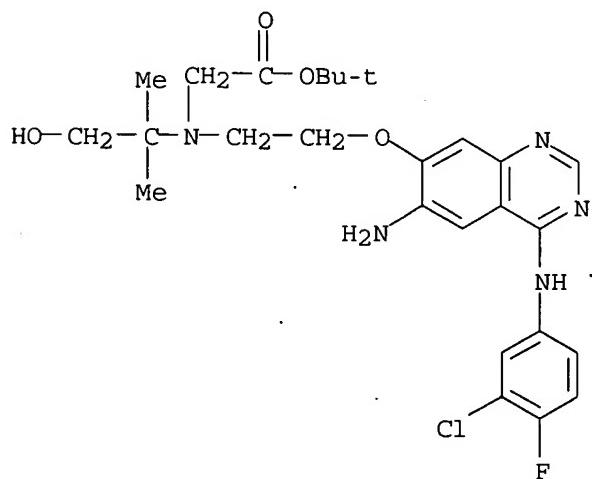
Absolute stereochemistry.





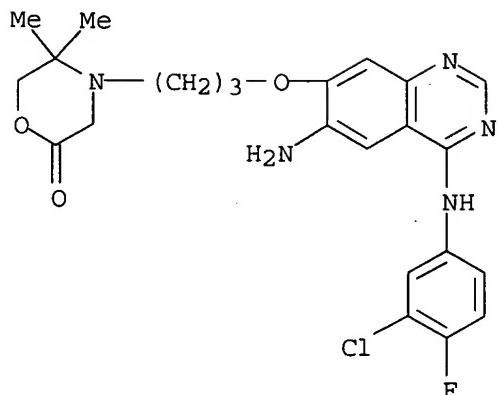
RN 402723-64-2 CAPLUS

CN Glycine, N-[2-[[6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl]oxy]ethyl]-N-(2-hydroxy-1,1-dimethylethyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



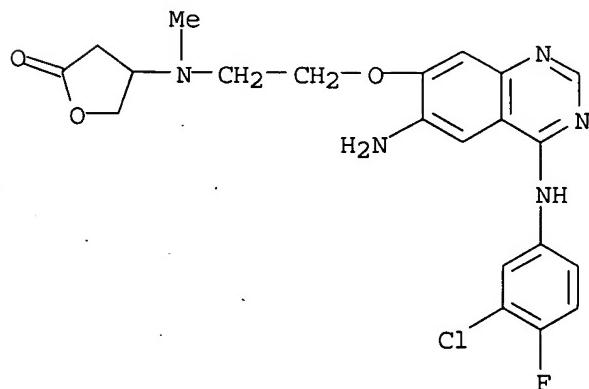
RN 402723-94-8 CAPLUS

CN 2-Morpholinone, 4-[3-[[6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl]oxy]propyl]-5,5-dimethyl- (9CI) (CA INDEX NAME)



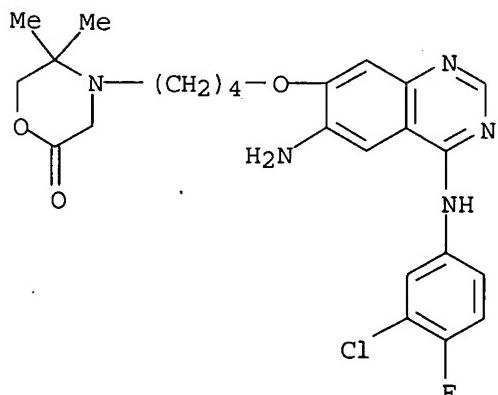
RN 402723-95-9 CAPLUS

CN 2(3H)-Furanone, 4-[[2-[[6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl]oxy]ethyl]methylamino]dihydro- (9CI) (CA INDEX NAME)



RN 402723-96-0 CAPLUS

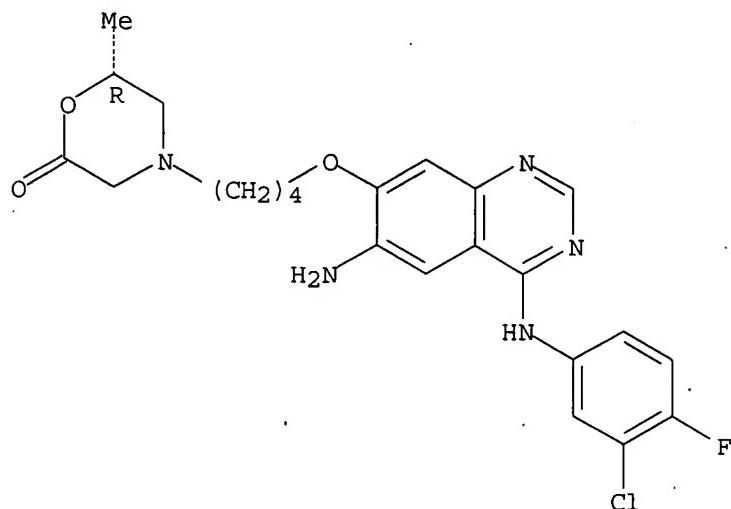
CN 2-Morpholinone, 4-[[4-[[6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl]oxy]butyl]methylamino]dihydro- (9CI) (CA INDEX NAME)



RN 402723-97-1 CAPLUS

CN 2-Morpholinone, 4-[4-[(6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl]oxy]butyl]-6-methyl-, (6R)- (9CI) (CA INDEX NAME)

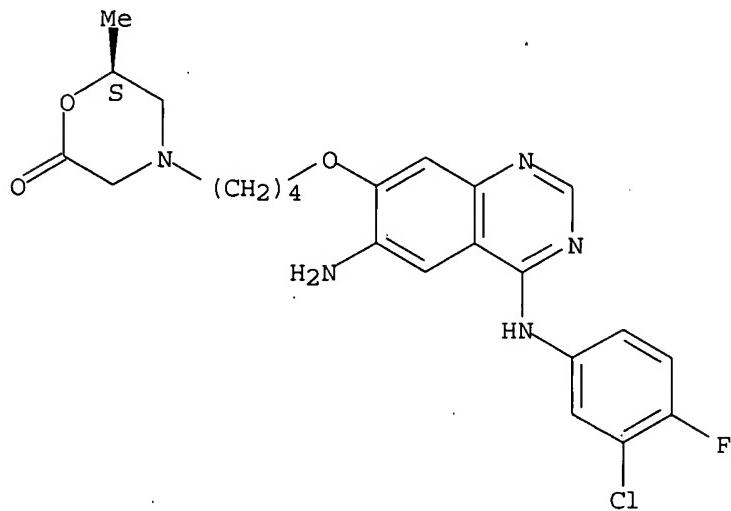
Absolute stereochemistry.



RN 402723-98-2 CAPLUS

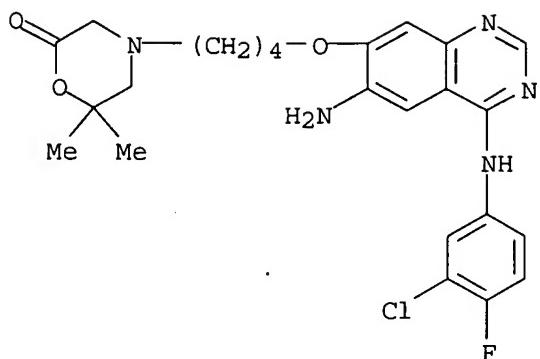
CN 2-Morpholinone, 4-[4-[(6-amino-4-[(3-chloro-4-fluorophényle)amino]-7-quinazolinyl)oxy]butyl]-6-methyl-, (6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



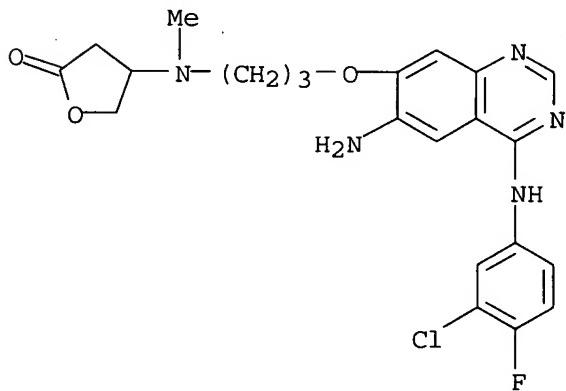
RN 402723-99-3 CAPLUS

CN 2-Morpholinone, 4-[4-[(6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl)oxy]butyl]-6,6-dimethyl- (9CI) (CA INDEX NAME)

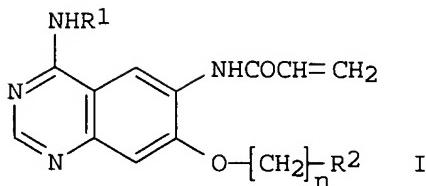


RN 402724-00-9 CAPLUS

CN 2(3H)-Furanone, 4-[3-[[6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl]oxy]propyl]methylamino]dihydro- (9CI) (CA INDEX NAME)



GI



AB Title compds. [I; R₁ = PhCH₂, 1-phenylethyl, (substituted) Ph; R₂ = N-(2-oxotetrahydrofuran-4-yl)methylamino, N(CH₂CO₂R₃)₂, (substituted) R₄OCOCH₂NCH₂CH₂OH, 2-oxomorpholin-4-yl; R₃ = H, Me, Et; R₄ = H, alkyl; n = 2-4], were prep'd. Thus, a mixt. of CH₂:CHCO₂H and Et₃N was stirred for 1 h at -50.degree. with CH₂:CHCO₂Cl in THF followed by addn. of 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(2,2-dimethyl-6-oxomorpholin-4-yl)propyloxy]quinazoline (prepn. given) in THF at -55.degree. and slowly heating up at 0.degree. up to completely conversion to give 60% 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(2,2-dimethyl-6-

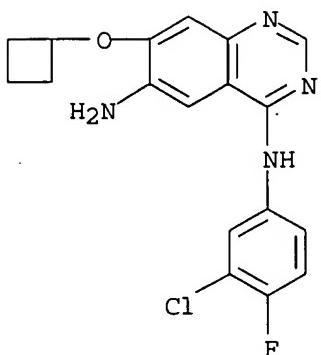
oxomorpholin-4-yl)propyloxy] -6-[(vinylcarbonyl)amino]quinazoline. One of the exemplified examples, 4-[(R)-(1-phenylethyl)amino]-7-[2-(2,2-dimethyl-6-oxomorpholin-4-yl)ethoxy]-6-[(vinylcarbonyl)amino]quinazoline, inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERC cells with IC₅₀ = 0.4 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

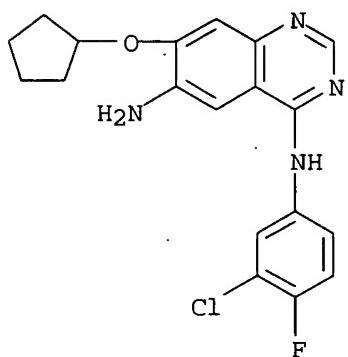
L4 ANSWER 5 OF 24 CAPLUS COPYRIGHT 2003 ACS
AN 2002:171889 CAPLUS
DN 136:232315
TI Preparation of 4-amino-6-vinylcarbonylaminoquinazolines as epidermal growth factor receptor signal transduction inhibitors
IN Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PA Boehringer Ingelheim Pharma Kg, Germany
SO PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002018373	A1	20020307	WO 2001-EP9537	20010818
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US	2002077330	A1	20020620	US 2001-929931	20010815
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				US 2000-230389PP	20000906
AU	2001084021	A5	20020313	AU 2001-84021	20010818
				DE 2000-10042060A	20000826
				WO 2001-EP9537 W	20010818
EP	1315717	A1	20030604	EP 2001-962953	20010818
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OS	MARPAT 136:232315				
IT	290303-28-5P 290303-32-1P 290304-07-3P				
	314771-75-0P 314771-76-1P 314771-77-2P				
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	402855-05-4P				
	RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)				
	(prepn. of (amino) (vinylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)				
RN	290303-28-5 CAPLUS				
CN	4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-(cyclobutyloxy)-				

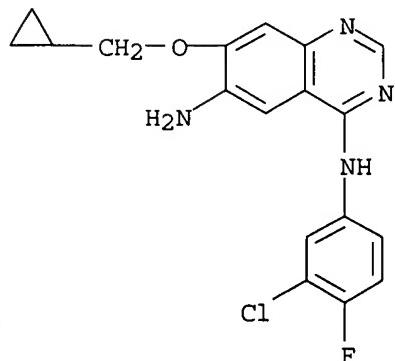
(9CI) (CA INDEX NAME)



RN 290303-32-1 CAPLUS

CN 4,6-Quinazolininediamine, N4- (3-chloro-4-fluorophenyl) -7- (cyclopentyloxy) -
(9CI) (CA INDEX NAME)

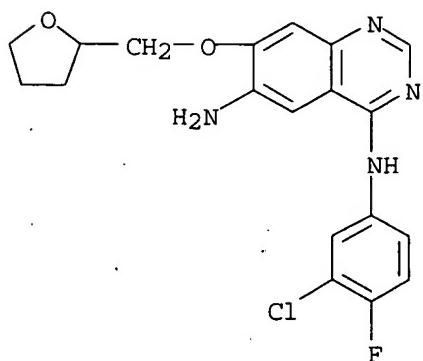
RN 290304-07-3 CAPLUS

CN 4,6-Quinazolininediamine, N4- (3-chloro-4-fluorophenyl) -7-
(cyclopropylmethoxy) - (9CI) (CA INDEX NAME)

RN 314771-75-0 CAPLUS

CN 4,6-Quinazolininediamine, N4- (3-chloro-4-fluorophenyl) -7- [(tetrahydro-2-

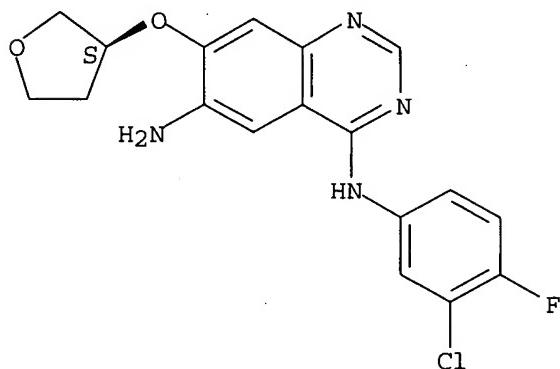
furanyl)methoxy] - (9CI) (CA INDEX NAME)



RN 314771-76-1 CAPLUS

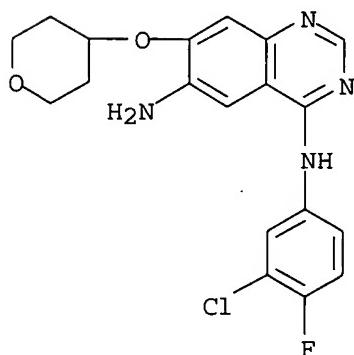
CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-[(3S)-tetrahydro-3-furanyl]oxy] - (9CI) (CA INDEX NAME)

Absolute stereochemistry.

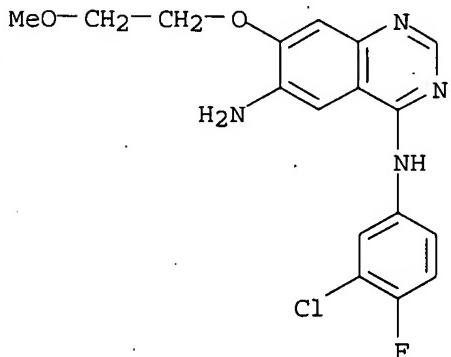


RN 314771-77-2 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-[(tetrahydro-2H-pyran-4-yl)oxy] - (9CI) (CA INDEX NAME)



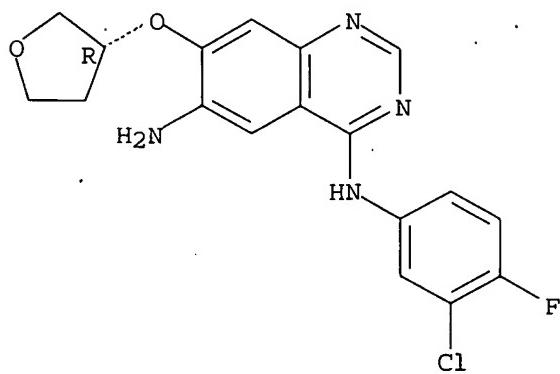
RN 402855-01-0 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-(2-methoxyethoxy)-
(9CI) (CA INDEX NAME)

RN 402855-03-2 CAPLUS

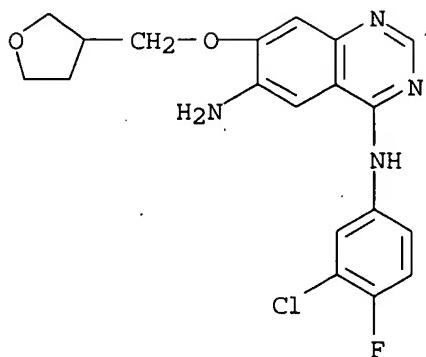
CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-[(3R)-tetrahydro-3-furanyl]oxy]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



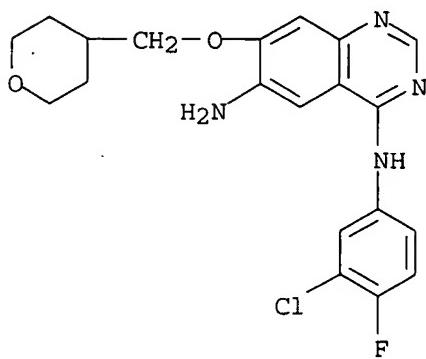
RN 402855-04-3 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-[(tetrahydro-3-furanyl)methoxy]- (9CI) (CA INDEX NAME)

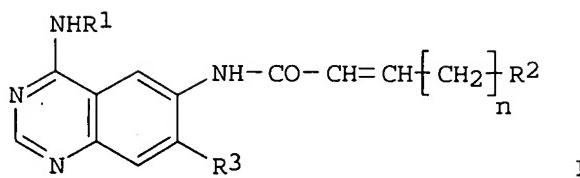


RN 402855-05-4 CAPLUS

CN 4,6-Quinazolinediamine, N4- (3-chloro-4-fluorophenyl) -7- [(tetrahydro-2H-pyran-4-yl)methoxy] - (9CI) (CA INDEX NAME)



GI



I

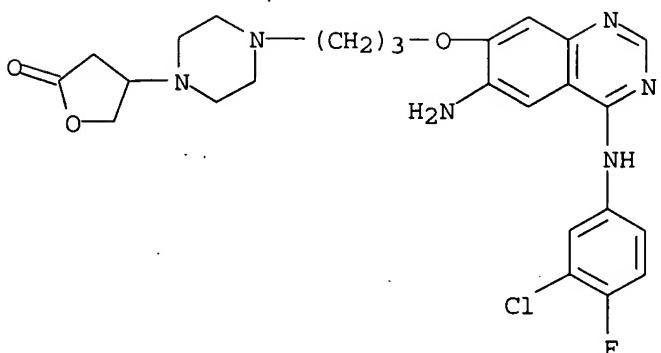
AB Title compds. [I; R1 = PhCH₂, 1-phenylethyl, (substituted) Ph; R2 = N-[(1,3-dioxolan-2-yl)methyl]methylamino, (substituted) R₄OCOCH₂NCH₂CH₂OH, 2-oxomorpholin-4-yl; R4 = H, alkyl; R3 = H, (alkoxy)alkoxy, cycloalkylalkoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrofuranylmethoxy, tetrahydropyranylmethoxy; n = 1-3], were prep'd. Thus, a mixt. of 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-cyclopropylmethoxyquinazoline (prepn. given) and diisopropylethylamine in THF was dropwise treated under ice-cooling with BrCH₂CH:CHCO₂Cl (prepn. given) in CH₂Cl₂ followed by stirring for 1 h under ice-cooling and for 2 h at room temp. and addn. of (S)-(2-hydroxypropylamino)acetic acid tert-Bu ester in CH₂Cl₂ to give after stirring over night at room temp. and stirring for 5 h at 60.degree.

64% 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-[N-(tert-butyloxycarbonylmethyl)-N-((S)-2-hydroxyprop-1-yl)amino]-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline. Several I inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERC cells with IC₅₀ = 0.02-15 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 24 CAPLUS COPYRIGHT 2003 ACS
AN 2002:171886 CAPLUS
DN 136:216758
TI Preparation of 4-amino-6-heterocyclcarbonylaminoquinazolines as epidermal growth factor receptor signal transduction inhibitors
IN Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PA Boehringer Ingelheim Pharma Kg, Germany
SO PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

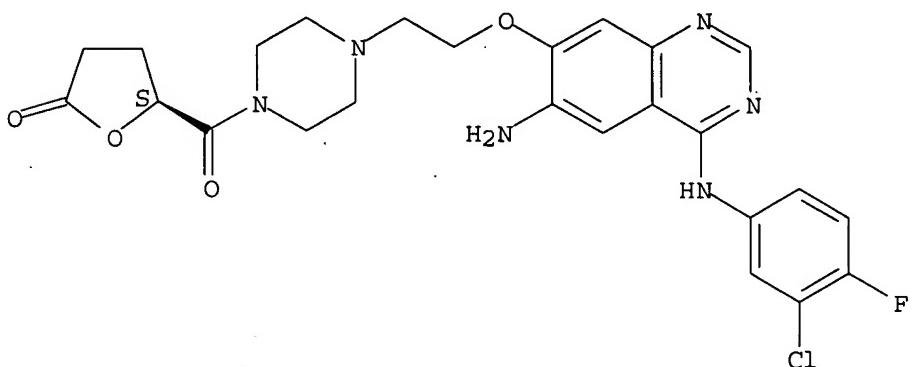
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002018370	A1	20020307	WO 2001-EP9535	20010818
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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DE	10042061	A1	20020307	DE 2000-10042061	20000826
AU	2001089814	A5	20020313	AU 2001-89814	20010818
				DE 2000-10042061A	20000826
				WO 2001-EP9535 W	20010818
EP	1315716	A1	20030604	EP 2001-969610	20010818
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			DE 2000-10042061A	20000826
				WO 2001-EP9535 W	20010818
US	2002082270	A1	20020627	US 2001-934753	20010822
				DE 2000-10042061A	20000826
				US 2000-230119PP	20000905
OS	MARPAT	136:216758			
IT	402496-48-4P 402496-50-8P 402496-52-0P				
	402496-81-5P 402496-83-7P 402497-08-9P				
	RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)				
	(prepn. of (amino) (heterocyclcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)				
RN	402496-48-4	CAPLUS			
CN	2 (3H)-Furanone, 4-[4-[3-[[6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl]oxy]propyl]-1-piperazinyl]dihydro-	(9CI)	(CA INDEX NAME)		



RN 402496-50-8 CAPLUS

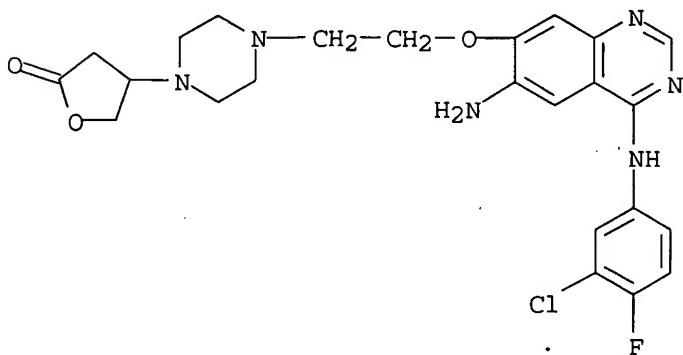
CN Piperazine, 1-[2-[[6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl]oxy]ethyl]-4-[(2S)-tetrahydro-5-oxo-2-furanyl]carbonyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 402496-52-0 CAPLUS

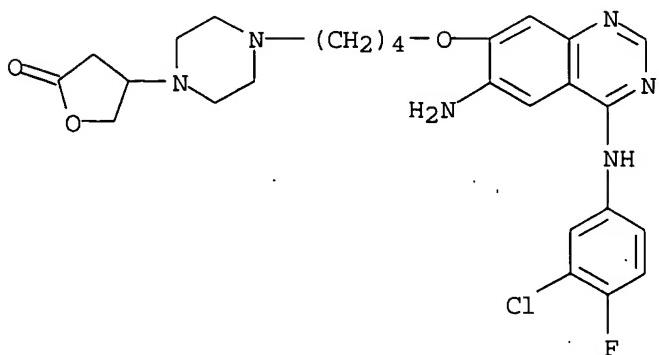
CN 2(3H)-Furanone, 4-[4-[[6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl]oxy]ethyl]-1-piperazinyl]dihydro- (9CI) (CA INDEX NAME)



RN 402496-81-5 CAPLUS

CN 2(3H)-Furanone, 4-[4-[[6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-

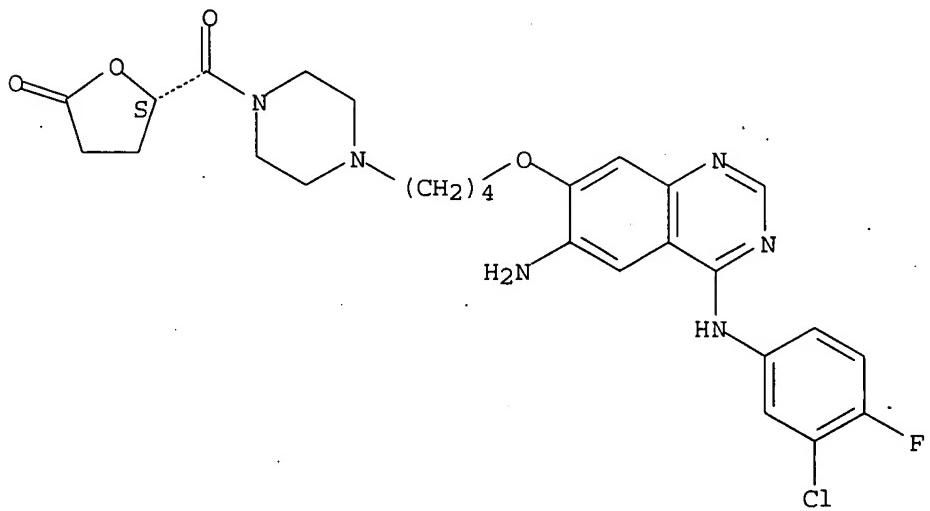
quinazolinyl]oxy]butyl]-1-piperazinyl)dihydro- (9CI) (CA INDEX NAME)



RN 402496-83-7 CAPLUS

CN Piperazine, 1-[4-[[6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl]oxy]butyl]-4-[(2S)-tetrahydro-5-oxo-2-furanyl]carbonyl]- (9CI) (CA INDEX NAME)

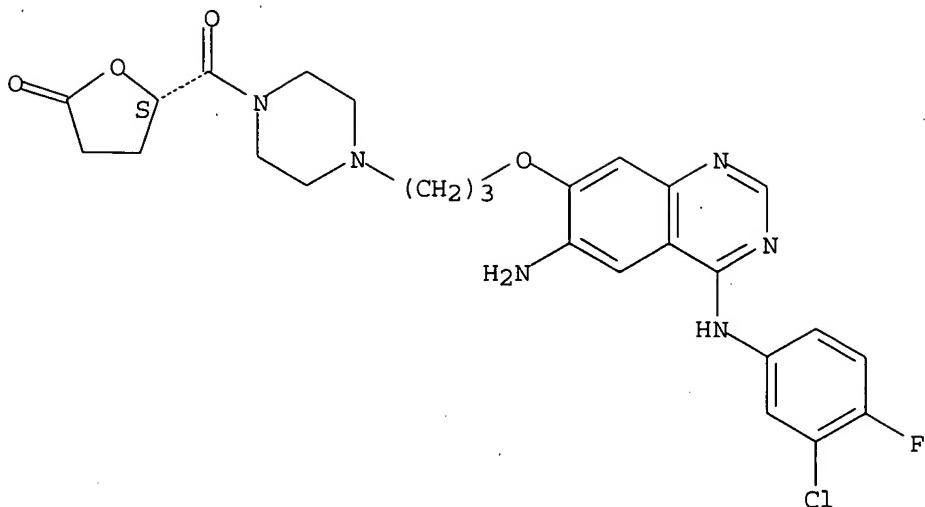
Absolute stereochemistry.



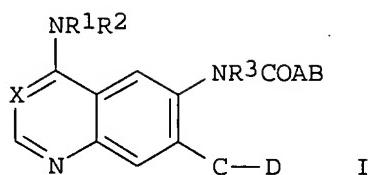
RN 402497-08-9 CAPLUS

CN Piperazine, 1-[3-[[6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-quinazolinyl]oxy]propyl]-4-[(2S)-tetrahydro-5-oxo-2-furanyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



GI



AB Title compds. [I; X = N, (substituted) methynyl; R1 = H, Me; R2 = (substituted) Ph, PhCH₂, 1-phenylethyl; R3 = H, Me; A = (substituted) vinyl, ethynyl, 1,3-butadien-1,4-yl; B = H, (substituted) alkyl, alkylcarbonyl, CO₂H, alkoxy carbonyl, aminocarbonyl, (di)alkylaminocarbonyl, pyrrolidinyl carbonyl, piperidinyl carbonyl, morpholinocarbonyl, alkylpiperazinyl carbonyl; C = (oxy)alkenyl, O; D = (substituted) pyrrolidinyl, piperidinyl, hexahydroazepinyl, piperazinyl, etc.], were prep'd. Thus, a mixt. of CH₂:CHCO₂H and Et₃N was stirred for 45 min at -50.degree. with CH₂:CHCO₂Cl in THF followed by dropwise addn. of 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-(3-[4-(2-oxotetrahydrofuran-4-yl)piperazin-1-yl]propoxy)quinazoline (prepn. given) in THF for 20 min and stirring at 0.degree. up to completely conversion to give 31% 4-[(3-chloro-4-fluorophenyl)amino]-7-(3-[4-(2-oxotetrahydrofuran-4-yl)piperazin-1-yl]propoxy)-6-[(vinylcarbonyl)amino]quinazoline. The latter inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERC cells with IC₅₀ = 12 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 24 CAPLUS COPYRIGHT 2003 ACS
AN 2001:762992 CAPLUS
DN 135:303907

TI Preparation of quinazolines as inhibitors of epidermal growth factor-mediated signal transduction.
 IN Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
 PA Boehringer Ingelheim Pharma K.-G., Germany
 SO PCT Int. Appl., 95 pp.
 CODEN: PIXXD2
 DT Patent
 LA German
 FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001077104	A1	20011018	WO 2001-EP3694	20010331
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			DE 2000-10017539A	20000408
				DE 2000-10040525A	20000818
DE	10017539	A1	20011011	DE 2000-10017539	20000408
DE	10040525	A1	20020228	DE 2000-10040525	20000818
EP	1280798	A1	20030205	EP 2001-938076	20010331
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			DE 2000-10017539A	20000408
				DE 2000-10040525A	20000818
				WO 2001-EP3694 W	20010331

PATENT FAMILY INFORMATION:

FAN 2001:747043

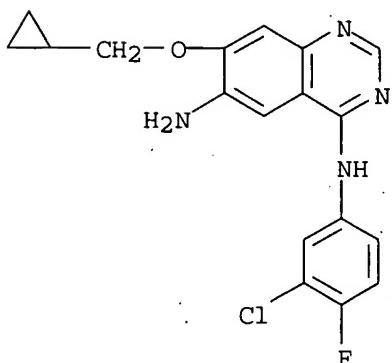
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 10017539	A1	20011011	DE 2000-10017539	20000408
	US 2001044435	A1	20011122	US 2001-816003	20010323
	WO 2001077104	A1	20011018	DE 2000-10017539A	20000408
				DE 2000-10040525A	20000818
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				DE 2000-10040525A	20000818
EP	1280798	A1	20030205	EP 2001-938076	20010331
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			DE 2000-10017539A	20000408
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				WO 2001-EP3694 W	20010331

OS MARPAT 135:303907

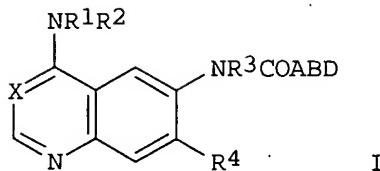
IT 290304-07-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)(prepn. of quinazolines as inhibitors of epidermal growth
factor-mediated signal transduction)

RN 290304-07-3 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-
(cyclopropylmethoxy) - (9CI) (CA INDEX NAME)

GI



AB Title compds. [I; X = NCN, N; R1 = H, alkyl; R2 = (substituted) Ph, PhCH2, PhCH2CH2; R3 = H, alkyl; R4 = H, alkoxy, cycloalkoxy, cycloalkylalkoxy; A = (substituted) vinylene; B = bond, (fluoro)alkylene; D = substituted pyrrolidinyl, piperidinyl, piperazinyl, etc.], were prep'd. Thus, 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-(piperazin-1-yl)-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline (prepn. given) in THF was treated with Et3N and then with 3-bromodihydrofuran-2-one in THF under ice cooling followed by stirring for 48 h at room temp. to give 56% 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-[4-(2-oxotetrahydrofuran-3-yl)piperazin-1-yl]-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline. The latter inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERc cells with IC50 = 0.05 nM.

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 24 CAPLUS COPYRIGHT 2003 ACS

AN 2001:747043 CAPLUS

DN 135:303901

TI Bicyclic heterocycles as inhibitors of epidermal growth factor receptor

mediated signal transduction
 IN Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
 PA Boehringer Ingelheim Pharma KG, Germany
 SO Ger. Offen., 28 pp.
 CODEN: GWXXBX
 DT Patent
 LA German
 FAN. CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 10017539	A1	20011011	DE 2000-10017539	20000408
	US 2001044435	A1	20011122	US 2001-816003	20010323
				DE 2000-10017539A	20000408
				DE 2000-10040525A	20000818
	WO 2001077104	A1	20011018	WO 2001-EP3694	20010331
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				DE 2000-10040525A	20000818
	EP 1280798	A1	20030205	EP 2001-938076	20010331
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
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				DE 2000-10040525A	20000818
				WO 2001-EP3694	W 20010331

PATENT FAMILY INFORMATION:

FAN 2001:762992

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	DE 10017539	A1	20011011	DE 2000-10017539	20000408	
	DE 10040525	A1	20020228	DE 2000-10040525	20000818	
	EP 1280798	A1	20030205	EP 2001-938076	20010331	
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
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				WO 2001-EP3694	W 20010331	

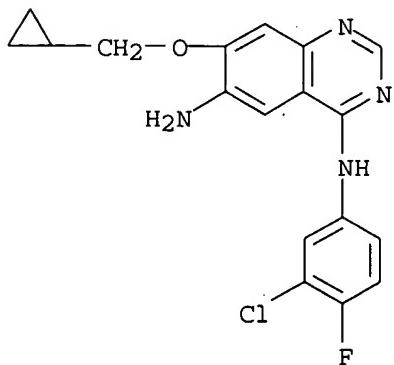
OS MARPAT 135:303901

IT 290304-07-3P

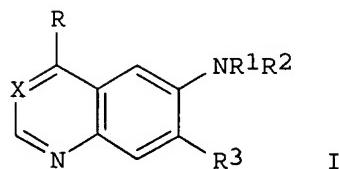
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (prep. of bicyclic heterocycles as inhibitors of epidermal growth factor receptor mediated signal transduction)

RN 290304-07-3 CAPLUS

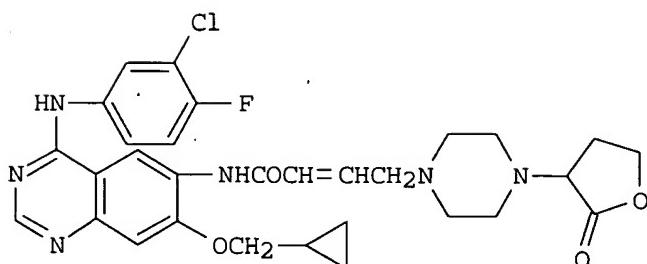
CN 4,6-Quinazoliniediamine, N4-(3-chloro-4-fluorophenyl)-7-(cyclopropylmethoxy) - (9CI) (CA INDEX NAME)



GI



I



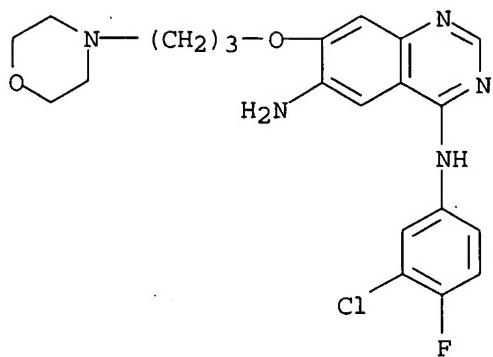
II

AB Bicyclic heterocycles I [X = N, CCN; R = substituted NH₂; R¹ = H, alkyl; R² = acyl; R³ = H, (un)substituted alkoxy, cycloalkoxy, tetrahydrofuryl oxy, tetrahydropyran oxy, tetrahydrofuranylmethoxy, tetrahydropyranylmethoxy] were prep'd. for use as inhibitors of tyrosine kinase-mediated signal transduction for treatment of tumors and diseases of the lung and airway. Thus, 4-[(3-chloro-4-fluorophenyl)amino]-7-fluoro-6-nitroquinazoline was treated with cyclopropylmethanol, followed by redn. to the amine, reaction with 4-bromocrotonic acid and N-tert.-

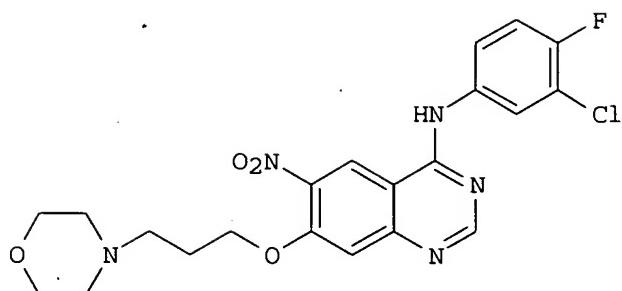
butoxycarbonylpiperazine, and deblocking to give the quinazoline II. II had an IC50 for inhibition of epidermal growth factor dependent proliferation of 0.05 nM.

L4 ANSWER 9 OF 24 CAPLUS COPYRIGHT 2003 ACS
 AN 2001:636060 CAPLUS
 DN 135:211054
 TI Method for the simplified production of N-(3-chloro-4-fluorophenyl)-N-[7-[3-(4-morpholinyl)propoxy]-6-nitroquinazolin-4-yl]amine or N-(3-chloro-4-fluorophenyl)-N-[7-[3-(4-morpholinyl)propoxy]-6-aminoquinazolin-4-yl]-amine
 IN Barth, Hubert; Steiner, Klaus; Schneider, Simon
 PA Goedecke G.m.b.H., Germany
 SO PCT Int. Appl., 13 pp.
 CODEN: PIXXD2
 DT Patent
 LA German
 FAN.CNT 1

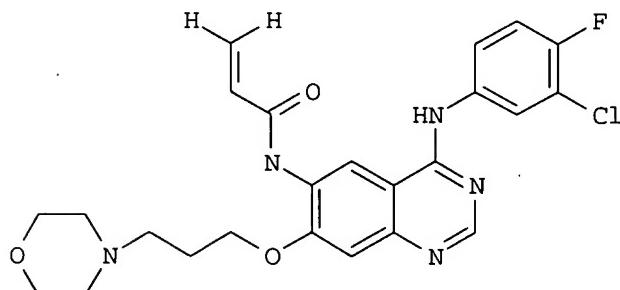
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001062743	A2	20010830	WO 2001-EP695	20010123
	WO 2001062743	A3	20020314		
		W:	AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG		DE 2000-10009267A 20000226
	DE 10009267	A1	20010830	DE 2000-10009267	20000226
	BR 2001008695	A	20021210	BR 2001-8695	20010123
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				WO 2001-EP695	W 20010123
EP	1265874	A2	20021218	EP 2001-953631	20010123
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR		DE 2000-10009267A 20000226	
	US 2003050313	A1	20030313	WO 2001-EP695	W 20010123
				US 2002-204911	20020826
				DE 2000-10009267A 20000226	
				WO 2001-EP695	W 20010123
OS	CASREACT 135:211054				
IT	267243-68-5P				
	RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)				
	(method for the simplified prodn. of N-(3-chloro-4-fluorophenyl)-N-[7-[3-(4-morpholinyl)propoxy]-6-nitroquinazolin-4-yl]amine or N-(3-chloro-4-fluorophenyl)-N-[7-[3-(4-morpholinyl)propoxy]-6-aminoquinazolin-4-yl]-amine)				
RN	267243-68-5 CAPLUS				
CN	4,6-Quinazolinediamine, N4-(3-chloro-4-fluorophenyl)-7-[3-(4-morpholinyl)propoxy] - (9CI) (CA INDEX NAME)				



GI



I



II

AB N-(3-chloro-4-fluorophenyl)-N-[7-[3-(4-morpholinyl)propoxy]-6-nitroquinazolin-4-yl]amine (I) or N-(3-chloro-4-fluorophenyl)-N-[7-[3-(4-morpholinyl)propoxy]-6-aminoquinazolin-4-yl]amine (II) are prep'd. in high yield and selectivity by the chlorination of 7-fluoro-6-nitroquinazolin-4(3H)-one with thionyl chloride to give 4-chloro-7-fluoro-6-nitroquinazoline which is condensed with 3-(4-morpholinyl)-1-propanol to give I which is then hydrogenated (e.g., using Raney nickel) into II.

L4 ANSWER 10 OF 24 CAPLUS COPYRIGHT 2003 ACS

AN 2001:380438 CAPLUS

DN 135:24657

TI Selective cellular targeting: multifunctional delivery vehicles

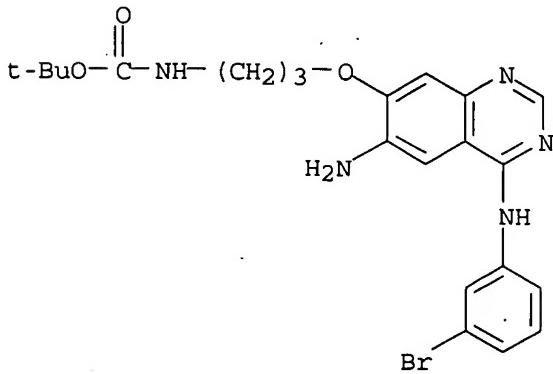
IN Glazier, Arnold

PA Drug Innovation + Design, Inc., USA

SO PCT Int. Appl., 981 pp.
CODEN: PIXXD2

DT Patent
LA English
FAN CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001036003	A2	20010525	WO 2000-US31262	20001114
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			US 2000-239478PP	20001011
				US 2000-241937PP	20001020
AU	2001016075	A5	20010530	AU 2001-16075	20001114
				US 1999-165485PP	19991115
				US 2000-239478PP	20001011
				US 2000-241937PP	20001020
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EP	1255567	A1	20021113	EP 2000-978631	20001114
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			US 1999-165485PP	19991115
				US 2000-239478PP	20001011
				US 2000-241937PP	20001020
				WO 2000-US31262W	20001114
IT	341551-80-2P				
	RL: PNU (Preparation, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)				
	(multifunctional delivery vehicles for selective cellular targeting of drugs)				
RN	341551-80-2 CAPLUS				
CN	Carbamic acid, [3-[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)				

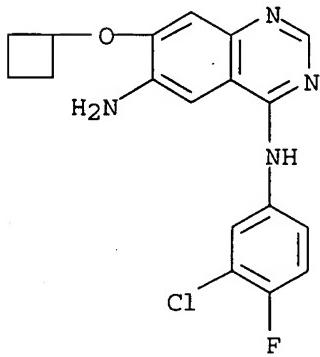


AB The present invention relates to the compns., methods, and applications of a novel approach to selective cellular targeting. The purpose of this invention is to enable the selective delivery and/or selective activation of effector mols. to target cells for diagnostic or therapeutic purposes. The present invention relates to multi-functional prodrugs or targeting vehicles wherein each functionality is capable of enhancing targeting selectivity, affinity, intracellular transport, activation or detoxification. The present invention also relates to ultralow dose, multiple target, multiple drug chemotherapy and targeted immunotherapy for cancer treatment.

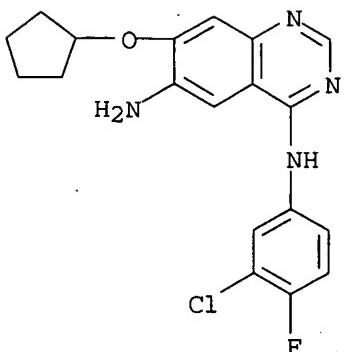
L4 ANSWER 11 OF 24 CAPLUS COPYRIGHT 2003 ACS
 AN 2000:911231 CAPLUS
 DN 134:71599
 TI Preparation of aminoquinazolines and aminoquinolines as epidermal growth factor receptor signal transduction inhibitors.
 IN Himmelsbach, Frank; Langkopf, Elke; Metz, Thomas; Solca, Flavio; Jung, Birgit; Baum, Anke
 PA Boehringer Ingelheim Pharma K.-G., Germany
 SO PCT Int. Appl., 104 pp.
 CODEN: PIXXD2
 DT Patent
 LA German
 FAN.CNT 1

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PI	WO 2000078735	A1	20001228	WO 2000-EP5547	20000616
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					US 1999-146644PP 19990730
					DE 2000-10023085A 20000511
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	DE 10023085	A1	20011115	DE 2000-10023085	20000511
	BR 2000011834	A	20020312	BR 2000-11834	20000616
					DE 1999-19928281A 19990621
					DE 2000-10023085A 20000511
					WO 2000-EP5547 W 20000616
	EP 1194418	A1	20020410	EP 2000-936888	20000616
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	JP 2003502410	T2	20030121	JP 2001-504901	20000616
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					US 1999-146644PP 19990730
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	EE 200100695	A	20030217	EE 2001-695	20000616

			DE 1999-19928281A 19990621
			US 1999-146644PP 19990730
			DE 2000-10023085A 20000511
			WO 2000-EP5547 W 20000616
BG 106189	A	20020830	BG 2001-106189 20011207
			DE 1999-19928281A 19990621
			US 1999-146644PP 19990730
			DE 2000-10023085A 20000511
			WO 2000-EP5547 W 20000616
US 2002169180	A1	20021114	US 2001-16280 20011210
			DE 1999-19928281A 19990621
			US 1999-146644PP 19990730
			DE 2000-10023085A 20000511
NO 2001006185	A	20011218	NO 2001-6185 20011218
			DE 1999-19928281A 19990621
			US 1999-146644PP 19990730
			DE 2000-10023085A 20000511
			WO 2000-EP5547 W 20000616
OS	MARPAT 134:71599		
IT	290303-28-5P 290303-32-1P 290304-07-3P 314771-70-5P 314771-71-6P 314771-72-7P 314771-73-8P 314771-74-9P 314771-75-0P 314771-76-1P 314771-77-2P 314771-80-7P 314771-81-8P		
	RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)		
	(prep. of aminoquinazolines and aminoquinolines as epidermal growth factor receptor signal transduction inhibitors)		
RN	290303-28-5 CAPLUS		
CN	4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-(cyclobutyloxy) - (9CI) (CA INDEX NAME)		

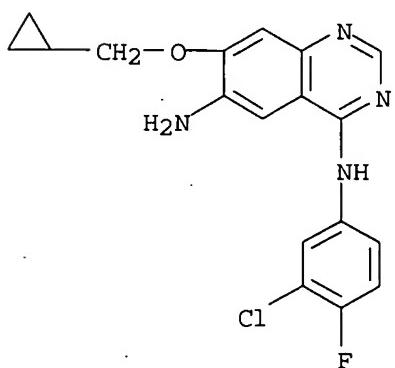


RN 290303-32-1 CAPLUS
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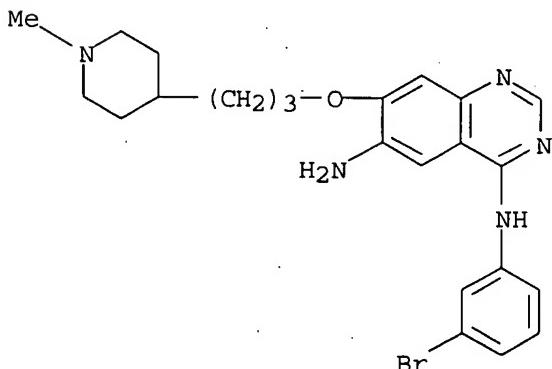
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CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-(cyclopropylmethoxy)- (9CI) (CA INDEX NAME)



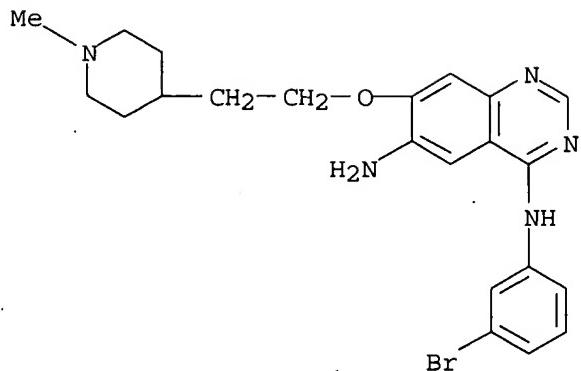
RN 314771-70-5 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-bromophenyl)-7-[3-(1-methyl-4-piperidinyl)propoxy]- (9CI) (CA INDEX NAME)



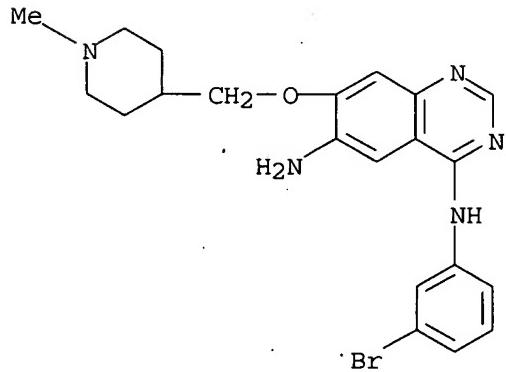
RN 314771-71-6 CAPLUS

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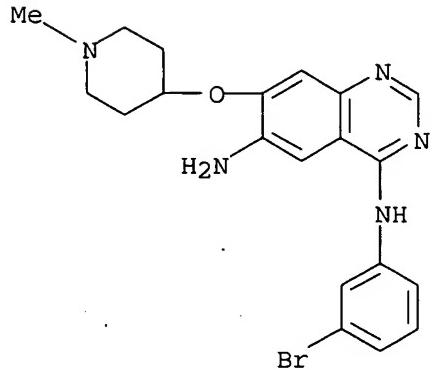
RN 314771-72-7 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-bromophenyl)-7-[(1-methyl-4-piperidinyl)methoxy] (9CI) (CA INDEX NAME)



RN 314771-73-8 CAPLUS

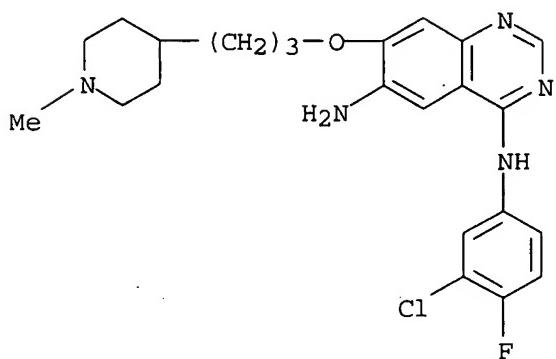
CN 4,6-Quinazolininediamine, N4-(3-bromophenyl)-7-[(1-methyl-4-piperidinyl)oxy] (9CI) (CA INDEX NAME)



RN 314771-74-9 CAPLUS

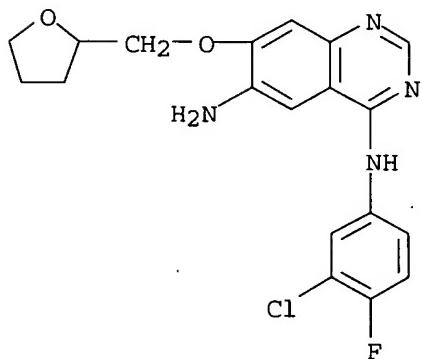
CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-[(1-methyl-4-

piperidinyl)propoxy] - (9CI) (CA INDEX NAME)



RN 314771-75-0 CAPLUS

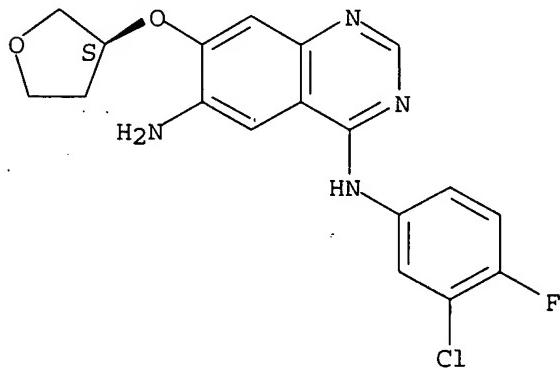
CN 4,6-Quinazolinediamine, N4-(3-chloro-4-fluorophenyl)-7-[(tetrahydro-2-furanyl)methoxy] - (9CI) (CA INDEX NAME)



RN 314771-76-1 CAPLUS

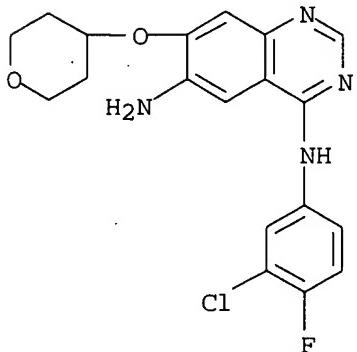
CN 4,6-Quinazolinediamine, N4-(3-chloro-4-fluorophenyl)-7-[(3S)-tetrahydro-3-furanyl]oxy] - (9CI) (CA INDEX NAME)

Absolute stereochemistry.



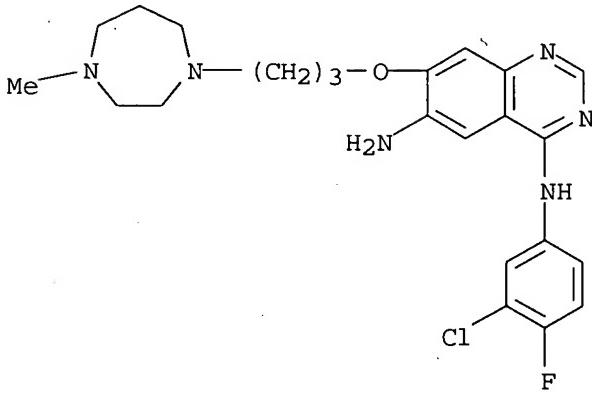
RN 314771-77-2 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-[(tetrahydro-2H-pyran-4-yl)oxy] - (9CI) (CA INDEX NAME)



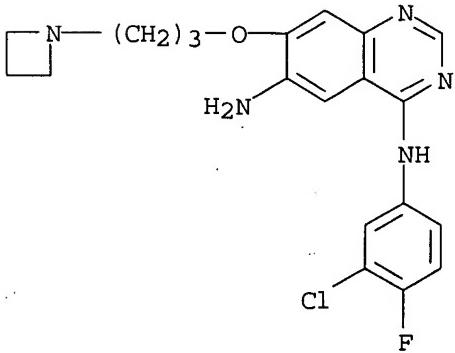
RN 314771-80-7 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-[3-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)propoxy] - (9CI) (CA INDEX NAME)

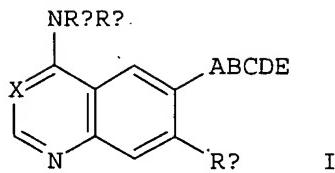


RN 314771-81-8 CAPLUS

CN 4,6-Quinazolininediamine, 7-[3-(1-azetidinyl)propoxy]-N4-(3-chloro-4-fluorophenyl) - (9CI) (CA INDEX NAME)



GI



AB Title compds. [I; Ra = H, alkyl; Rb = (substituted) Ph, PhCH₂, PhCH₂CH₂; Rc = (substituted) cycloalkoxy, cycloalkylalkoxy; A = (alkyl-substituted) imino; B = CO, SO₂; C = (substituted) allenylene, vinylene, butadienylene, ethynylene; D = (fluorinated) alkylene, carbonylalkylene, sulfonylalkylene, carbonyloxyalkylene, carbonyliminoalkylene, bond, etc.; E = amino, (substituted) alkylamino, dialkylamino, etc.], were prep'd. Thus, 6-amino-4-[(3-bromophenyl)amino]-7-[3-(1-methylpiperidin-4-yl)propoxy]quinazoline (prepn. given) in CH₂Cl₂ contg. Et₃N at -10. degree. was treated with acryloyl chloride in THF to give 35% 4-[(3-bromophenyl)amino]-7-[3-(1-methylpiperidin-4-yl)propyloxy]-6-[(vinylcarbonyl)amino]quinazoline. The latter inhibited EGF-dependent proliferation of F/L HERC cells with IC₅₀ = <0.35 nM.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 24 CAPLUS COPYRIGHT 2003 ACS

AN 2000:628125 CAPLUS

DN 133:207919

TI Preparation of 4-amino-quinazoline and quinoline derivatives having an inhibitory effect on signal transduction mediated by tyrosine kinases useful for treating tumoral diseases, lung and respiratory tract diseases

IN Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Metz, Thomas; Solca, Flavio; Blech, Stefan

PA Boehringer Ingelheim Pharma K.-G., Germany

SO PCT Int. Appl., 232 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000051991	A1	20000908	WO 2000-EP1496	20000224
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				DE 1999-19911366A	19990315
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				US 1999-149329PP	19990817
				DE 1999-19954816A	19991113

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DE 19928306	A1	20001228	DE 1999-19928306 19990621
DE 19954816	A1	20010517	DE 1999-19954816 19991113
CA 2361174	AA	20000908	CA 2000-2361174 20000224 DE 1999-19908567A 19990227 DE 1999-19911366A 19990315 DE 1999-19928306A 19990621 US 1999-149329PP 19990817 DE 1999-19954816A 19991113 WO 2000-EP1496 W 20000224 EP 2000-910695 20000224
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JP 2002538145	T2	20021112	DE 1999-19908567A 19990227 DE 1999-19911366A 19990315 DE 1999-19928306A 19990621 US 1999-149329PP 19990817 DE 1999-19954816A 19991113 WO 2000-EP1496 W 20000224 JP 2000-602218 20000224
EE 200100449	A	20021216	DE 1999-19908567A 19990227 DE 1999-19911366A 19990315 DE 1999-19928306A 19990621 US 1999-149329PP 19990817 DE 1999-19954816A 19991113 WO 2000-EP1496 W 20000224 EE 2001-449 20000224
BG 105765	A	20020329	DE 1999-19908567A 19990227 DE 1999-19911366A 19990315 DE 1999-19928306A 19990621 US 1999-149329PP 19990817 DE 1999-19954816A 19991113 WO 2000-EP1496 W 20000224 BG 2001-105765 20010801
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NO 2001004114	A	20011015	DE 1999-19908567A 19990227 DE 1999-19911366A 19990315 DE 1999-19928306A 19990621 US 1999-149329PP 19990817 DE 1999-19954816A 19991113 WO 2000-EP1496 W 20000224 NO 2001-4114 20010824
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 WO 2000-EP1496 W 20000224

PATENT FAMILY INFORMATION:

FAN 2000:607393

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19908567 CA 2361174	A1 AA	20000831 20000908	DE 1999-19908567 CA 2000-2361174 DE 1999-19908567A DE 1999-19911366A DE 1999-19928306A US 1999-149329PP DE 1999-19954816A WO 2000-EP1496	19990227 20000224 19990227 19990315 19990621 19990817 19991113 W 20000224
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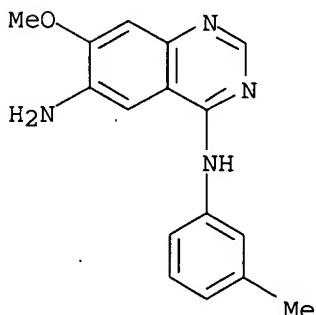
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IT 153437-17-3 290304-06-2 290304-07-3

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 (prepn. of aminoquinazoline and aminoquinoline derivs. having an inhibitory effect on signal transduction mediated by tyrosine kinases useful for treating tumoral diseases, lung and respiratory tract diseases)

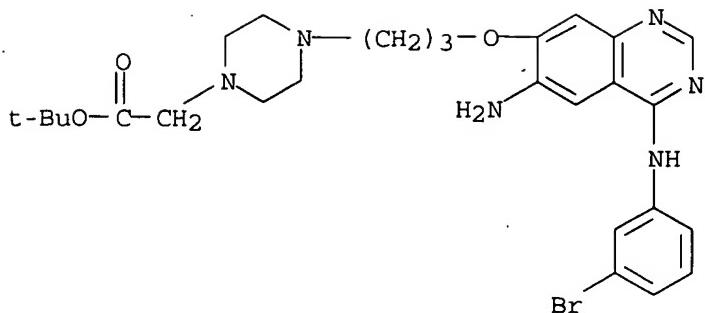
RN 153437-17-3 CAPLUS

CN 4,6-Quinazolinediamine, 7-methoxy-N4-(3-methylphenyl)- (9CI) (CA INDEX NAME)



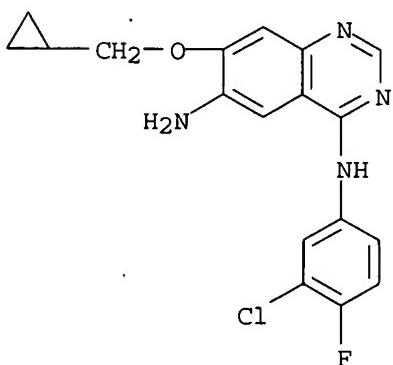
RN 290304-06-2 CAPLUS

CN 1-Piperazineacetic acid, 4-[3-[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 290304-07-3 CAPLUS

CN 4,6-Quinazolinediamine, N4-(3-chloro-4-fluorophenyl)-7-(cyclopropylmethoxy)- (9CI) (CA INDEX NAME)



IT 289700-72-7P 289700-73-8P 289700-74-9P

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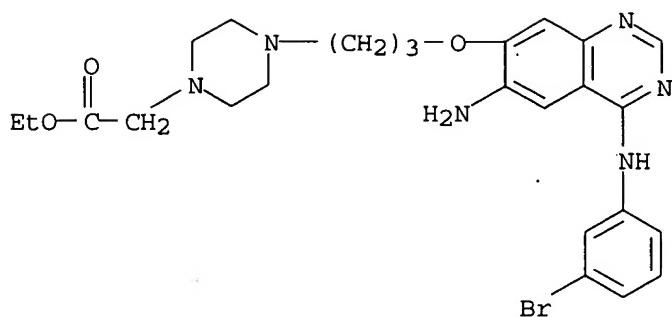
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RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

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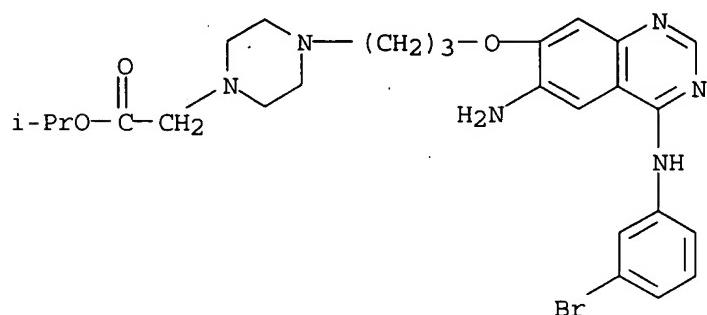
RN 289700-72-7 CAPLUS

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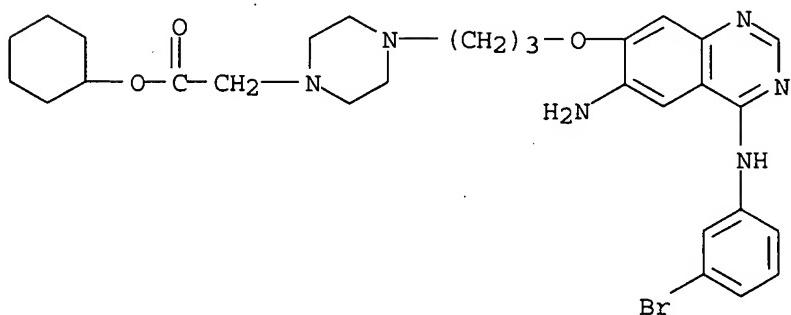
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CN 1-Piperazineacetic acid, 4-[3-[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]propyl]-, 1-methylethyl ester (9CI) (CA INDEX NAME)



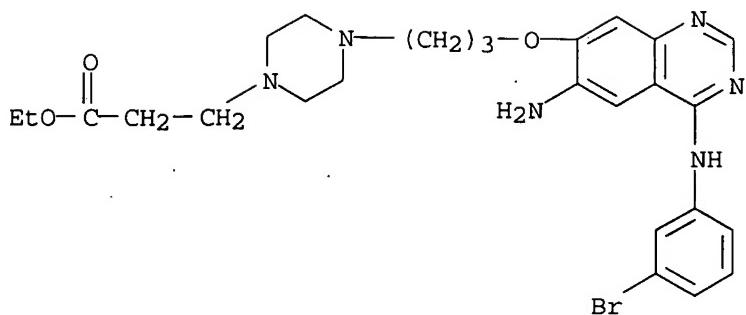
RN 289700-74-9 CAPLUS

CN 1-Piperazineacetic acid, 4-[3-[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]propyl]-, cyclohexyl ester (9CI) (CA INDEX NAME)



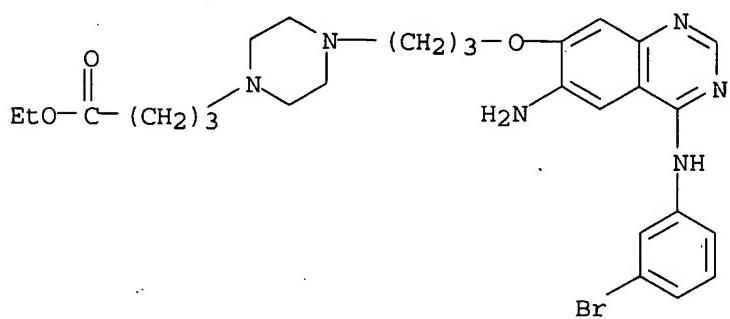
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CN 1-Piperazinepropanoic acid, 4-[3-[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]propyl]-, ethyl ester (9CI) (CA INDEX NAME)



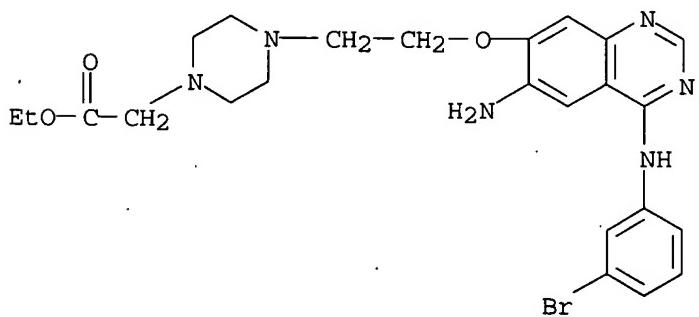
RN 289700-76-1 CAPLUS

CN 1-Piperazinebutanoic acid, 4-[3-[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]propyl]-, ethyl ester (9CI) (CA INDEX NAME)



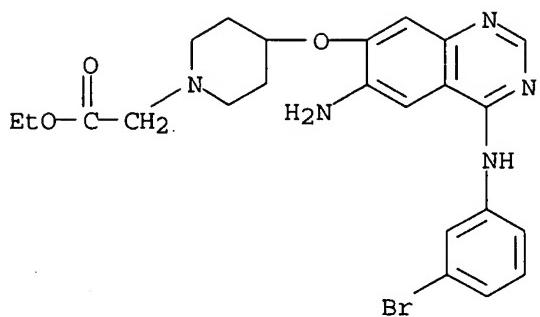
RN 289700-77-2 CAPLUS

CN 1-Piperazineacetic acid, 4-[2-[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]ethyl]-, ethyl ester (9CI) (CA INDEX NAME)



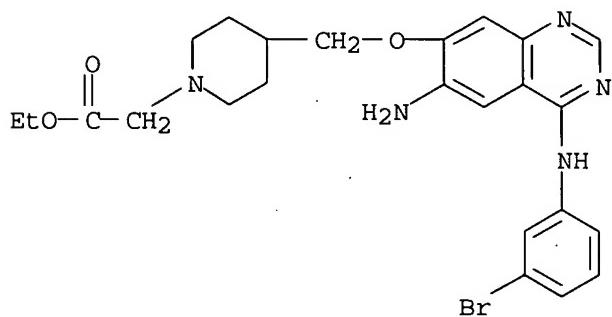
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CN 1-Piperidineacetic acid, 4-[[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]-, ethyl ester (9CI) (CA INDEX NAME)



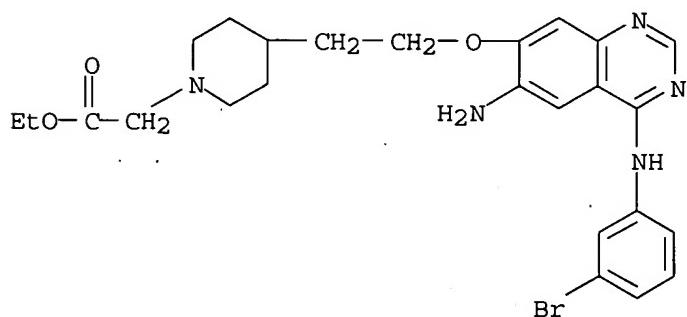
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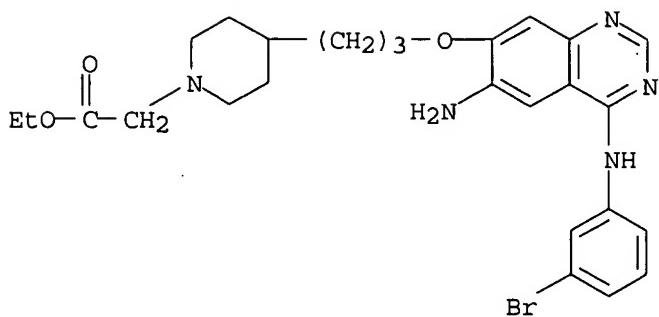
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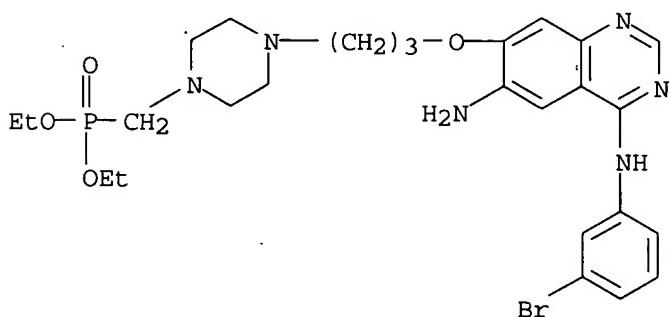
RN 289700-81-8 CAPLUS

CN 1-Piperidineacetic acid, 4-[[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxyl]propyl]-, ethyl ester (9CI) (CA INDEX NAME)



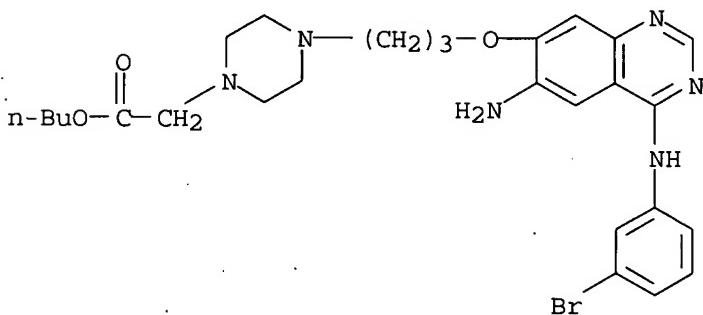
RN 290303-20-7 CAPLUS

CN Phosphonic acid, [[4-[3-[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]propyl]-1-piperazinyl]methyl], diethyl ester (9CI) (CA INDEX NAME)



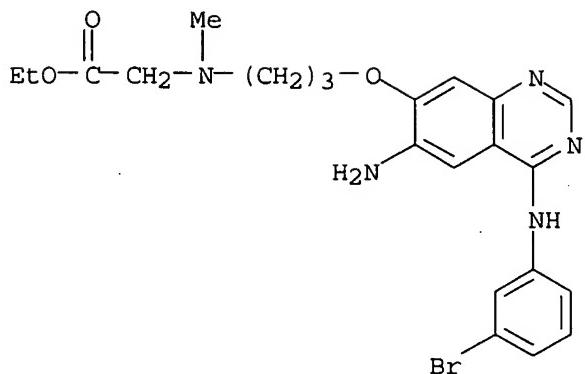
RN 290303-21-8 CAPLUS

CN 1-Piperazineacetic acid, 4-[3-[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]propyl]-, butyl ester (9CI) (CA INDEX NAME)



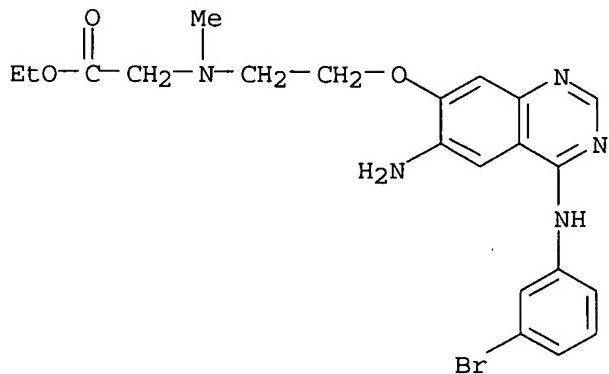
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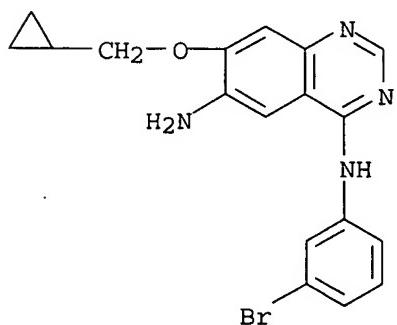
RN 290303-23-0 CAPLUS

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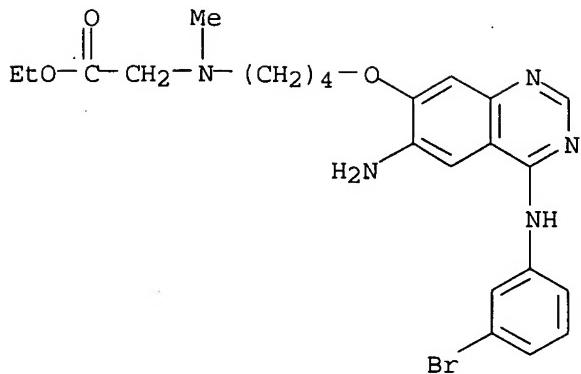
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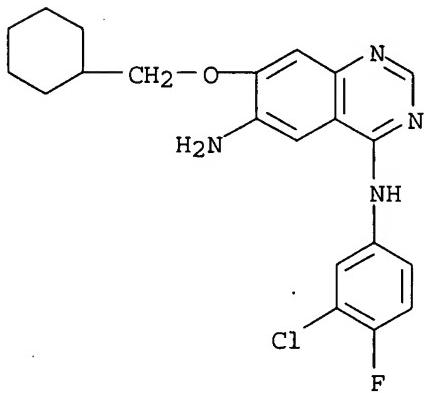


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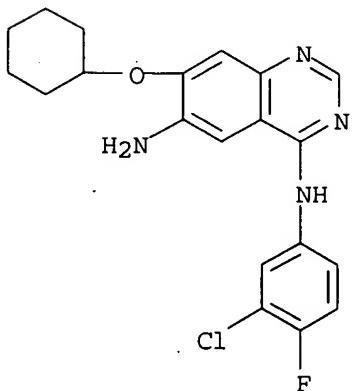
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RN 290303-26-3 CAPLUS

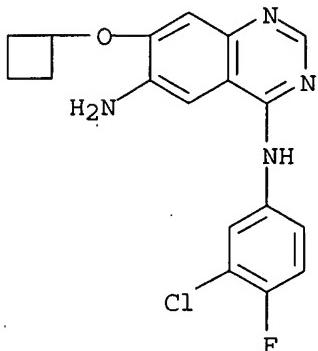
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(9CI) (CA INDEX NAME)

RN 290303-27-4 CAPLUS

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(9CI) (CA INDEX NAME)

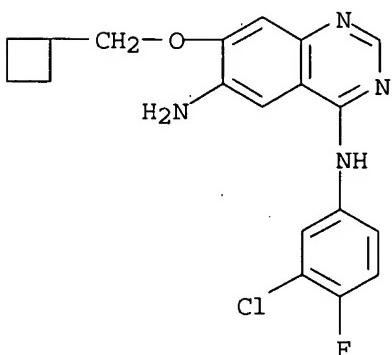
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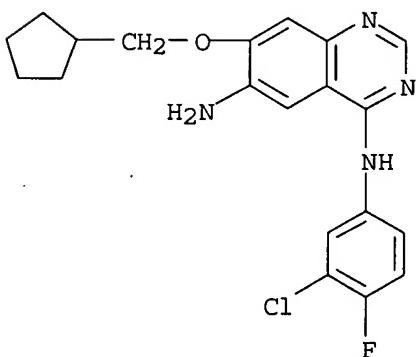
RN 290303-29-6 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-(cyclobutylmethoxy)-
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RN 290303-30-9 CAPLUS

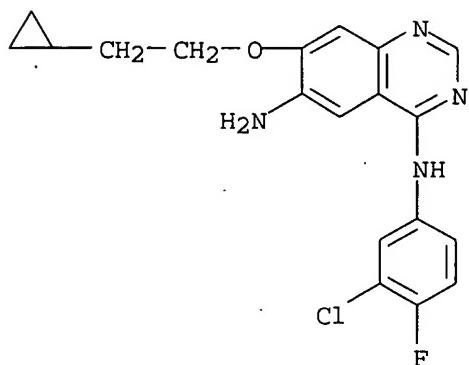
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RN 290303-31-0 CAPLUS

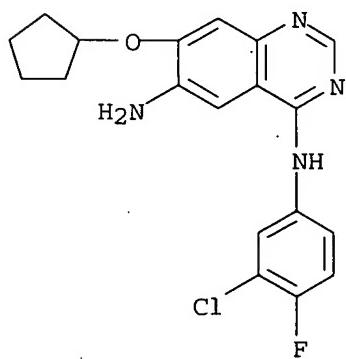
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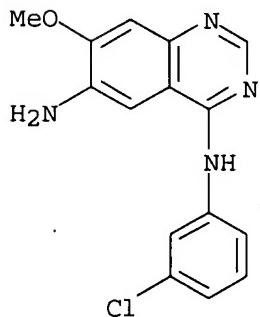
RN 290303-32-1 CAPLUS

CN 4,6-Quinazolinediamine, N4- (3-chloro-4-fluorophenyl) -7- (cyclopentyloxy) - (9CI) (CA INDEX NAME)



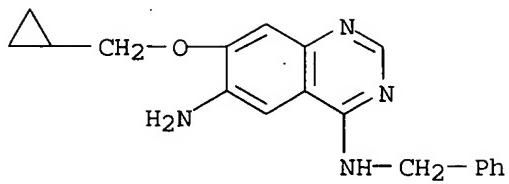
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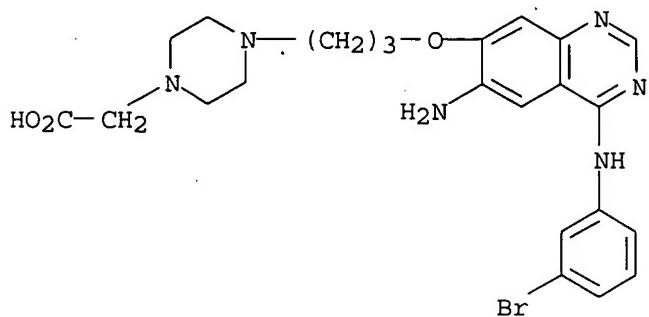
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CN 4,6-Quinazolinediamine, 7- (cyclopropylmethoxy) -N4- (phenylmethyl) - (9CI) (CA INDEX NAME)

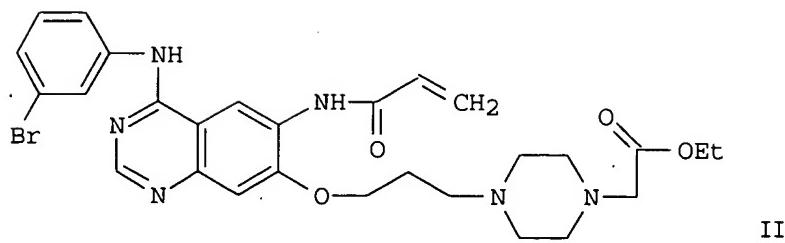
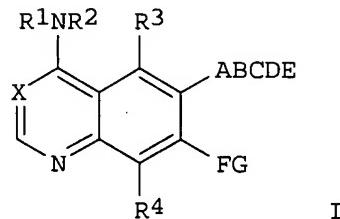


RN 290303-73-0 CAPLUS

CN 1-Piperazineacetic acid, 4-[3-[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]propyl]- (9CI) (CA INDEX NAME)



GI



AB Title compds. [I; R1 = H, C1-C4-alkyl; R2 = (un)substituted Ph, benzyl, 1-phenylethyl; R3, R4 independently = H, F, Cl, CH3O, CH3OCH2, (CH3)2NCH2, (CH3CH2)2NCH2, pyrrolidino, piperidino, morpholino; X = C(CN), N; A = O, NH, (C1-C4)-alkylN; B = CO, SO2; C = 1,3-allenylene, 1,1-vinylene, 1,2-vinylene, 1,3-butadien-1,4-ylene, with CH3, CF3 substitution; D = alkylene, CO-alkylene, SO2-alkylene; CO, SO2; E = HOCO(CH2)nNR5, (HO)2P(=O)(CH2)nNR5; n = 1-6; R5 = H, alkyl], tautomers, stereoisomers, and physiol. acceptable salts are prepd. and having valuable pharmacol. properties, particularly an inhibiting effect on signal transduction mediated by tyrosine kinases. Title compds. are useful for treating tumoral diseases, diseases of the lungs and respiratory tract. Thus, the title compd. II was prepd. and tested by Cell Titer 96TM Aq.

Nonradioactive Cell Proliferation Assay.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4	ANSWER 13 OF 24 CAPLUS COPYRIGHT 2003 ACS			
AN	2000:607393 CAPLUS			
DN	133:207916			
TI	Preparation of aminoquinazolines as epidermal growth factor receptor inhibitors.			
IN	Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Metz, Thomas			
PA	Boehringer Ingelheim Pharma K-G, Germany			
SO	Ger. Offen., 26 pp.			
	CODEN: GWXXBX			
DT	Patent			
LA	German			
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PATENT FAMILY INFORMATION:

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 US 1999-149329PP 19990817
 DE 1999-19954816A 19991113
 WO 2000-EP1496 W 20000224
 BG 105765 A 20020329 BG 2001-105765 20010801
 DE 1999-19908567A 19990227
 DE 1999-19911366A 19990315
 DE 1999-19928306A 19990621

HR 20010617	A1	20021031	US 1999-149329PP 19990817 DE 1999-19954816A 19991113 WO 2000-EP1496 W 20000224 HR 2001-617 20010823 DE 1999-19908567A 19990227 DE 1999-19911366A 19990315 DE 1999-19928306A 19990621 US 1999-149329PP 19990817 DE 1999-19954816A 19991113 WO 2000-EP1496 W 20000224
NO 2001004114	A	20011015	NO 2001-4114 20010824 DE 1999-19908567A 19990227 DE 1999-19911366A 19990315 DE 1999-19928306A 19990621 US 1999-149329PP 19990817 DE 1999-19954816A 19991113 WO 2000-EP1496 W 20000224

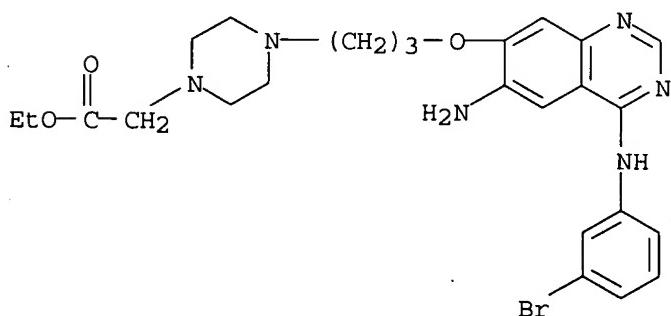
OS MARPAT 133:207916

IT 289700-72-7P 289700-73-8P 289700-74-9P
 289700-75-0P 289700-76-1P 289700-77-2P
 289700-78-3P 289700-79-4P 289700-80-7P
 289700-81-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (prepn. of aminoquinazolines as epidermal growth factor receptor inhibitors)

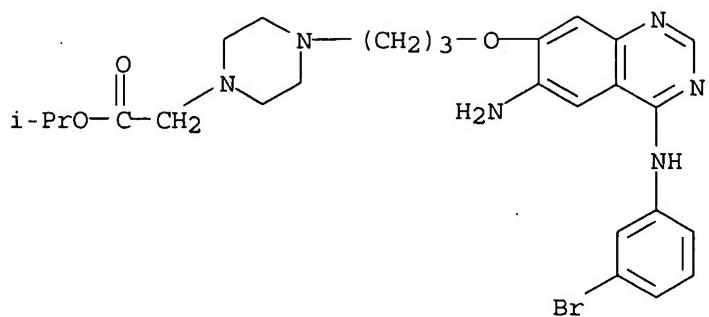
RN 289700-72-7 CAPLUS

CN 1-Piperazineacetic acid, 4-[3-[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]propyl]-, ethyl ester (9CI) (CA INDEX NAME)



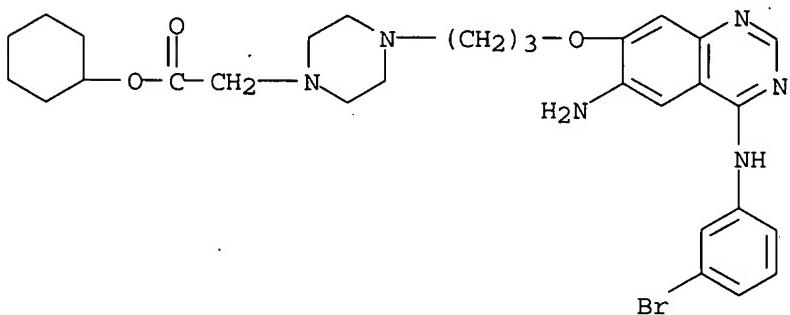
RN 289700-73-8 CAPLUS

CN 1-Piperazineacetic acid, 4-[3-[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]propyl]-, 1-methylethyl ester (9CI) (CA INDEX NAME)



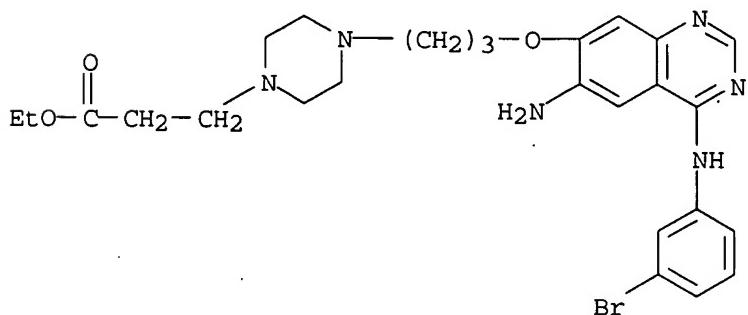
RN 289700-74-9 CAPLUS

CN 1-Piperazineacetic acid, 4-[3-[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]propyl]-, cyclohexyl ester (9CI) (CA INDEX NAME)



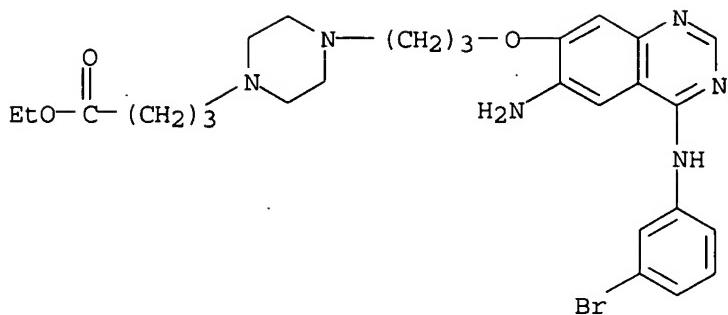
RN 289700-75-0 CAPLUS

CN 1-Piperazinepropanoic acid, 4-[3-[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]propyl]-, ethyl ester (9CI) (CA INDEX NAME)



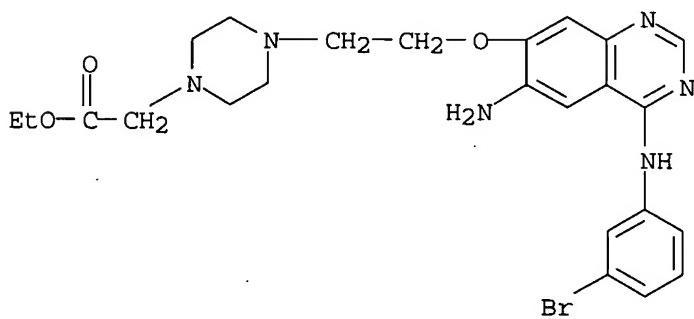
RN 289700-76-1 CAPLUS

CN 1-Piperazinebutanoic acid, 4-[3-[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]propyl]-, ethyl ester (9CI) (CA INDEX NAME)



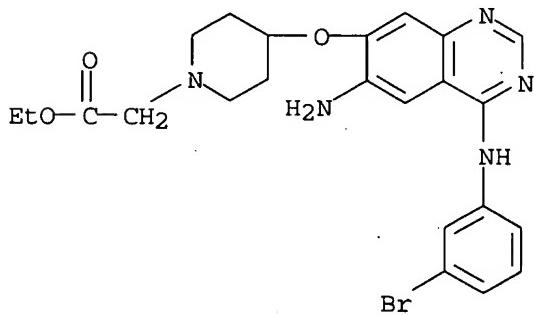
RN 289700-77-2 CAPLUS

CN 1-Piperazineacetic acid, 4-[2-[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]ethyl]-, ethyl ester (9CI) (CA INDEX NAME)



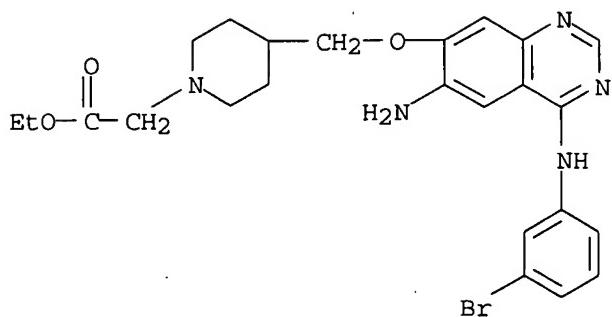
RN 289700-78-3 CAPLUS

CN 1-Piperidineacetic acid, 4-[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]-, ethyl ester (9CI) (CA INDEX NAME)



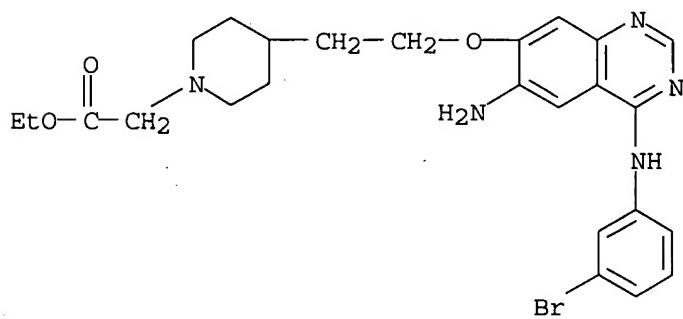
RN 289700-79-4 CAPLUS

CN 1-Piperidineacetic acid, 4-[[[6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]methyl]-, ethyl ester (9CI) (CA INDEX NAME)



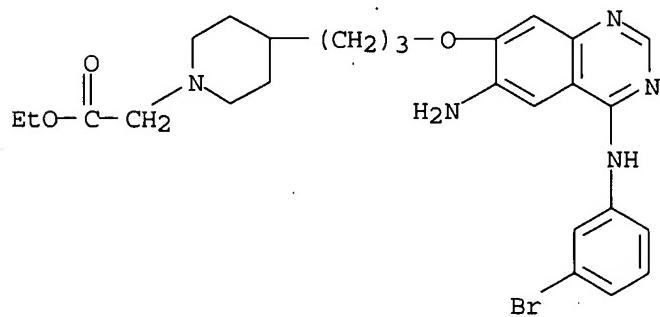
RN 289700-80-7 CAPLUS

CN 1-Piperidineacetic acid, 4-[2-[(6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]ethyl]-, ethyl ester (9CI) (CA INDEX NAME)

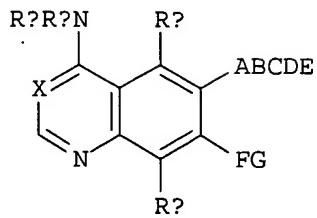


RN 289700-81-8 CAPLUS

CN 1-Piperidineacetic acid, 4-[3-[(6-amino-4-[(3-bromophenyl)amino]-7-quinazolinyl]oxy]propyl]-, ethyl ester (9CI) (CA INDEX NAME)



GI



AB Title compds. [I; Ra = H, alkyl; Rb = (substituted) Ph, PhCH₂, 1-phenylethyl; Rc, Rm = H, F, Cl, MeO, (methoxy-, dimethylamino-, diethylamino-, pyrrolidino-, piperidino-, morpholino- substituted) Me; X = N, NCC; A = O, alkylimino; B = CO, SO₂; C = (Me- or F₃C-substituted) allenylene, vinylene; D = (fluorinated) alkylene, carbonylalkylene, sulfonylalkylene, etc.; E, G = (substituted) R₆O₂CYNR₅, etc.; R₅ = H, (substituted) alkyl; R₆ = H, (substituted) alkyl, cycloalkyl, alkenyl, alkynyl, etc.; F = alkylene, oxyalkylene, O; FG = H, F, Cl, alkoxy, etc.], were prep'd. Thus, 6-amino-4-[(3-bromophenyl)amino]-7-[3-[4-(ethoxycarbonyl)methyl]piperazin-1-yl]propoxy]quinazoline (prepn. given) in CH₂Cl₂ contg. Et₃N was treated with acryloyl chloride in CH₂Cl₂ at -10.degree. to give 62% 4-[(3-bromophenyl)amino]-7-[3-[4-(ethoxycarbonyl)methyl]piperazin-1-yl]propyloxy]-6-[(vinylcarbonyl)amino]quinazoline. The latter inhibited EGF-dependent proliferation with IC₅₀ = 2.6 nM.

L4 ANSWER 14 OF 24 CAPLUS COPYRIGHT 2003 ACS

AN 2000:481416 CAPLUS

DN 134:216784

TI Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(phenylamino)quinazoline- and 4-(phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions. [Erratum to document cited in CA132:317628]

AU Smaill, Jeff B.; Newcastle, Gordon W.; Bridges, Alexander J.; Zhou, Hairong; Showalter, H. D. Hollis; Fry, David W.; Nelson, James M.; Sherwood, Veronika; Elliott, William L.; Vincent, Patrick W.; DeJohn, Dana E.; Loo, Joseph A.; Greis, Kenneth D.; Chan, O. Helen; Reyner, Eric L.; Lipka, Elke; Denny, William A.

CS Auckland Cancer Society Research Centre, Faculty Medical and Health Sciences, The Univ. Auckland, Auckland, N. Z.

SO Journal of Medicinal Chemistry (2000), 43(16), 3199
CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

LA English

IT 198961-78-3P 198961-84-1P 198961-86-3P

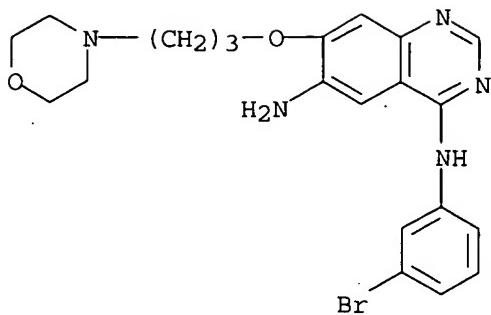
198961-87-4P 267243-67-4P 267243-68-5P

267243-69-6P

RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(antitumor and EGFR enzyme-inhibiting SAR of quinazolines (Erratum))

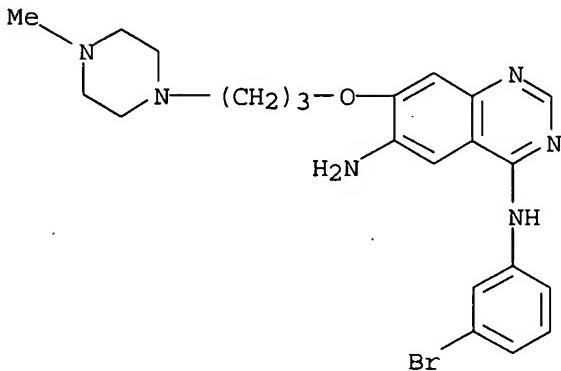
RN 198961-78-3 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-bromophenyl)-7-[3-(4-morpholinyl)propoxy]- (9CI) (CA INDEX NAME)



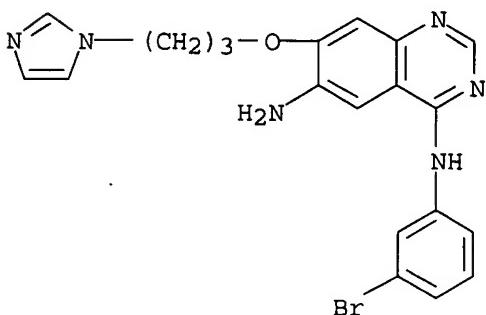
RN 198961-84-1 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-bromophenyl)-7-[3-(4-methyl-1-piperazinyl)propoxy] - (9CI) (CA INDEX NAME)



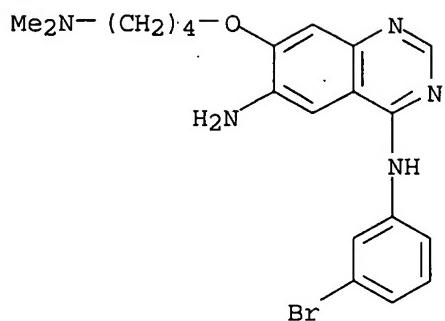
RN 198961-86-3 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-bromophenyl)-7-[3-(1H-imidazol-1-yl)propoxy] - (9CI) (CA INDEX NAME)



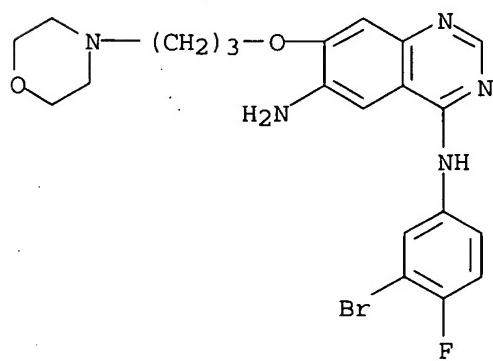
RN 198961-87-4 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-bromophenyl)-7-[4-(dimethylamino)butoxy] - (9CI) (CA INDEX NAME)



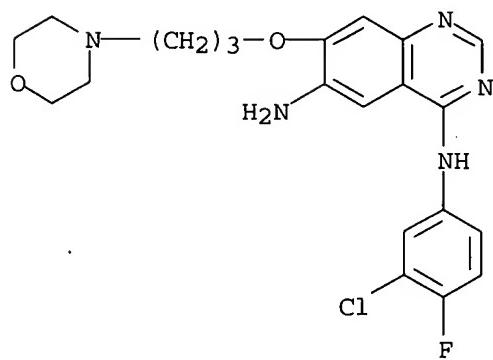
RN 267243-67-4 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-bromo-4-fluorophenyl)-7-[3-(4-morpholinyl)propoxy] - (9CI) (CA INDEX NAME)



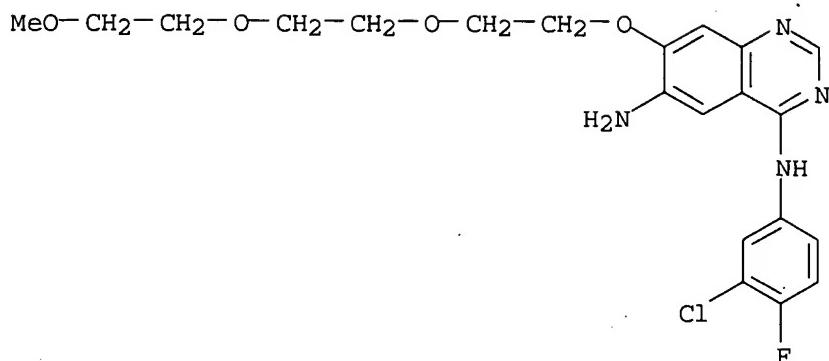
RN 267243-68-5 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-[3-(4-morpholinyl)propoxy] - (9CI) (CA INDEX NAME)



RN 267243-69-6 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy] - (9CI) (CA INDEX NAME)



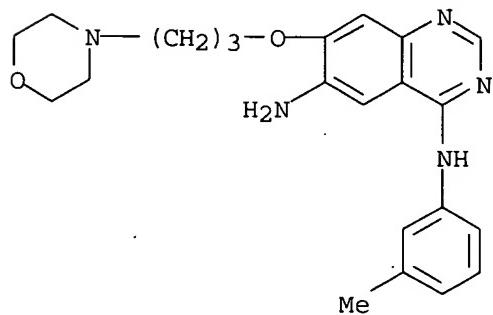
IT 198961-80-7P 198961-82-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(antitumor and EGFR enzyme-inhibiting SAR of quinazolines (Erratum))

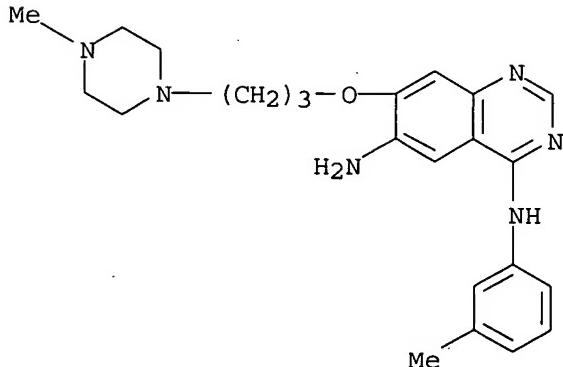
RN 198961-80-7 CAPLUS

CN 4,6-Quinazolinediamine, N4-(3-methylphenyl)-7-[3-(4-morpholinyl)propoxy]- (9CI) (CA INDEX NAME)



RN 198961-82-9 CAPLUS

CN 4,6-Quinazolinediamine, N4-(3-methylphenyl)-7-[3-(4-methyl-1-piperazinyl)propoxy]- (9CI) (CA INDEX NAME)



AB Six author names were inadvertently omitted from the author contribution

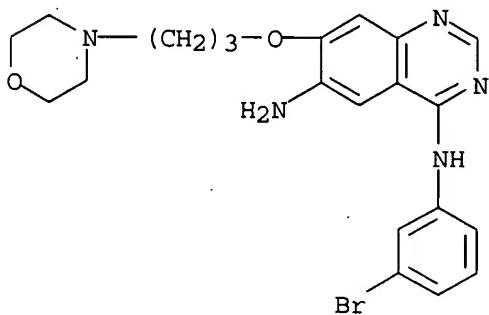
line. The complete author list is as follows: Jeff B. Smaill, Gordon W. Rewcastle, Alexander J. Bridges, Hairong Zhou, H. D. Hollis Showalter, David W. Fry, James M. Nelson, Veronika Sherwood, William L. Elliott, Patrick W. Vincent, Dana E. DeJohn, Joseph A. Loo, Kenneth D. Greis, O. Helen Chan, Eric L. Reyner, Elke Lipka, and William A. Denny.

L4 ANSWER 15 OF 24 CAPLUS COPYRIGHT 2003 ACS
 AN 2000:368316 CAPLUS
 DN 133:4672
 TI Preparation of N-{4-(3-chloro-4-fluorophenylamino)-7-[3-(morpholin-4-yl)propoxy]quinazolin-6-yl}acrylamide as an irreversible inhibitor of tyrosine kinases
 IN Bridges, Alexander James; Driscoll, Denise; Klohs, Wayne Daniel
 PA Warner-Lambert Co., USA
 SO PCT Int. Appl., 33 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

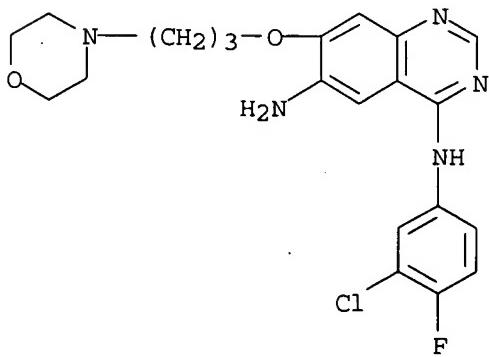
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000031048	A1	20000602	WO 1999-US22116	19990923
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	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU	9962612	A1	20000613	US 1998-109065PP	19981119
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				US 1998-109065PP	19981119
BR	9915487	A	20010731	WO 1999-US22116W	19990923
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				US 1998-109065PP	19981119
				WO 1999-US22116W	19990923
EP	1131304	A1	20010912	EP 1999-949821	19990923
EP	1131304	B1	20021204		
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				WO 1999-US22116W	19990923
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				WO 1999-US22116W	19990923
EE	200100271	A	20021015	EE 2001-271	19990923
				US 1998-109065PP	19981119
				WO 1999-US22116W	19990923
AT	229008	E	20021215	AT 1999-949821	19990923
				US 1998-109065PP	19981119
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US	6344455	B1	20020205	US 2001-831991	20010516
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				WO 1999-US22116W	19990923
NO	2001002465	A	20010713	NO 2001-2465	20010518
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US 1998-109065PP 19981119
WO 1999-US22116W 19990923

IT 198961-78-3P 267243-68-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of N-{4-(3-chloro-4-fluorophenylamino)-7-[3-(morpholin-4-yl)propoxy]quinazolin-6-yl}acrylamide as an irreversible inhibitor of tyrosine kinases)
RN 198961-78-3 CAPLUS
CN 4,6-Quinazolinediamine, N4-(3-bromophenyl)-7-[3-(4-morpholinyl)propoxy]- (9CI) (CA INDEX NAME)



RN 267243-68-5 CAPLUS
CN 4,6-Quinazolinediamine, N4-(3-chloro-4-fluorophenyl)-7-[3-(4-morpholinyl)propoxy]- (9CI) (CA INDEX NAME)



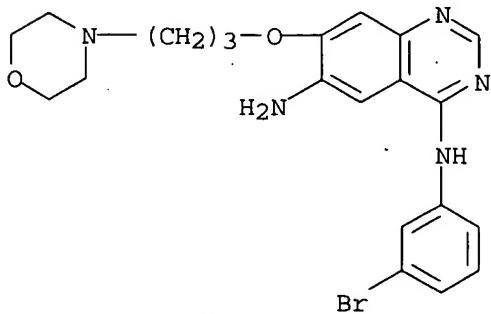
AB The title compd. that is an irreversible inhibitor of tyrosine kinases such as EGFR, erbB2, and erbB4, and inhibitor of the tyrosine phosphorylation of erbB3 and VEGF secretion (biol. data were given), was prep'd. The title compd. is useful in treating cancer, restenosis, atherosclerosis, endometriosis, and psoriasis.

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 24 CAPLUS COPYRIGHT 2003 ACS
AN 2000:164843 CAPLUS
DN 132:317628
TI Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(Phenylamino)quinazoline- and

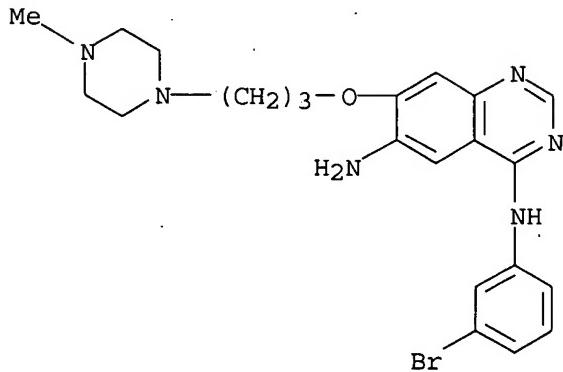
4-(Phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions

AU Smaill, Jeff B.; Newcastle, Gordon W.; Loo, Joseph A.; Greis, Kenneth D.; Chan, O. Helen; Reyner, Eric L.; Lipka, Elke; Showalter, H. D. Hollis; Vincent, Patrick W.; Elliott, William L.; Denny, William A.
 CS Auckland Cancer Society Research Centre Faculty of Medical and Health Sciences, The University of Auckland, Auckland, N. Z.
 SO Journal of Medicinal Chemistry (2000), 43(7), 1380-1397
 CODEN: JMCMAR; ISSN: 0022-2623
 PB American Chemical Society
 DT Journal
 LA English
 IT 198961-78-3P 198961-84-1P 198961-86-3P
 198961-87-4P 267243-67-4P 267243-68-5P
 267243-69-6P
 RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (antitumor and EGFR enzyme-inhibiting SAR of quinazolines)
 RN 198961-78-3 CAPLUS
 CN 4,6-Quinazolinediamine, N4-(3-bromophenyl)-7-[3-(4-morpholinyl)propoxy]- (9CI) (CA INDEX NAME)



RN 198961-84-1 CAPLUS

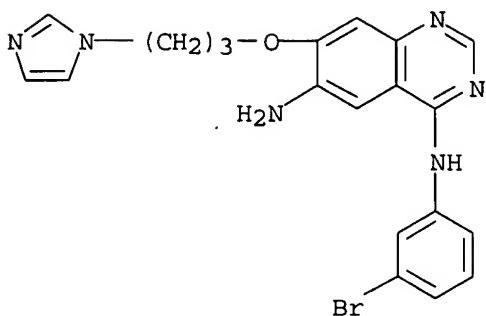
CN 4,6-Quinazolinediamine, N4-(3-bromophenyl)-7-[3-(4-methyl-1-piperazinyl)propoxy]- (9CI) (CA INDEX NAME)



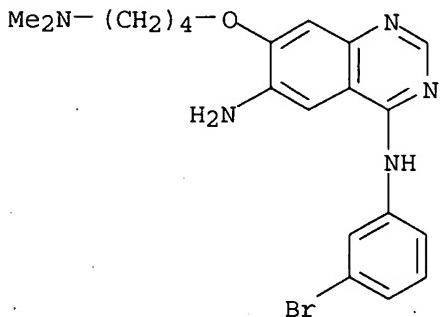
RN 198961-86-3 CAPLUS

CN 4,6-Quinazolinediamine, N4-(3-bromophenyl)-7-[3-(1H-imidazol-1-yl)propoxy]-

(9CI) (CA INDEX NAME)

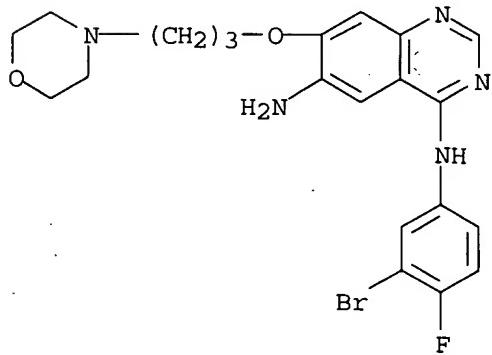


RN 198961-87-4 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-bromophenyl)-7-[4-(dimethylamino)butoxy] -
(9CI) (CA INDEX NAME)

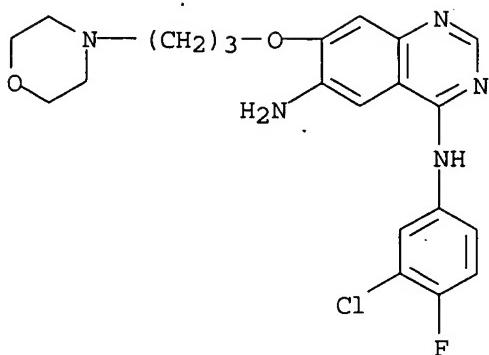
RN 267243-67-4 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-bromo-4-fluorophenyl)-7-[3-(4-morpholinyl)propoxy] - (9CI) (CA INDEX NAME)



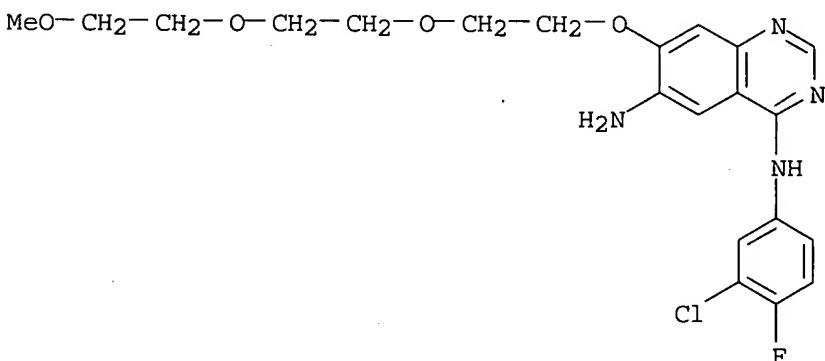
RN 267243-68-5 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-[3-(4-morpholinyl)propoxy] - (9CI) (CA INDEX NAME)



RN 267243-69-6 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-chloro-4-fluorophenyl)-7-[2-[2-(2-methoxyethoxy)ethoxy]- (9CI) (CA INDEX NAME)

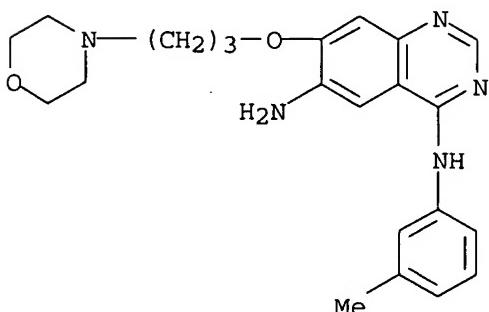


IT 198961-80-7P 198961-82-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(antitumor and EGFR enzyme-inhibiting SAR of quinazolines)

RN 198961-80-7 CAPLUS

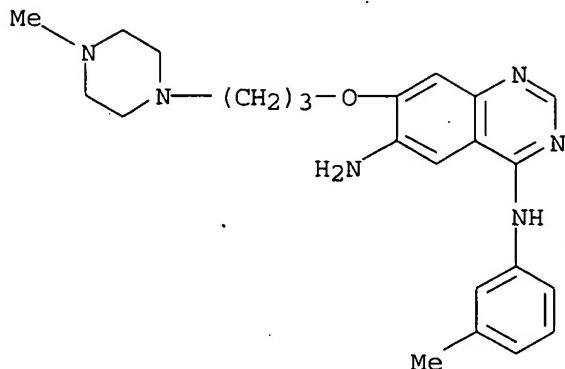
CN 4,6-Quinazolininediamine, N4-(3-methylphenyl)-7-[3-(4-morpholinyl)propoxy]- (9CI) (CA INDEX NAME)



RN 198961-82-9 CAPLUS

CN 4,6-Quinazolininediamine, N4-(3-methylphenyl)-7-[3-(4-methyl-1-

piperazinyl)propoxy] - (9CI) (CA INDEX NAME)

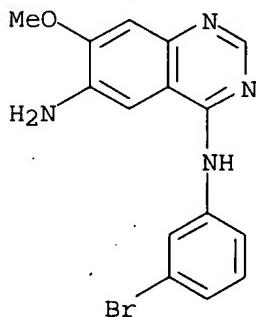


AB 4-Anilinoquinazoline- and 4-anilinopyrido[3,2-d]pyrimidine-6-acrylamides substituted with solubilizing 7-alkylamine or 7-alkoxyamine side chains were prep'd. by reaction of the corresponding 6-amines with acrylic acid or acrylic acid anhydrides. In the pyrido[3,2-d]pyrimidine series, the intermediate 6-amino-7-alkylamines were prep'd. from 7-bromo-6-fluoropyrido[3,2-d]pyrimidine via Stille coupling with the appropriate stannane under palladium(0) catalysis. This proved a versatile method for the introduction of cationic solubilizing side chains. The compds. were evaluated for their inhibition of phosphorylation of the isolated EGFR enzyme and for inhibition of EGF-stimulated autophosphorylation of EGFR in A431 cells and of heregulin-stimulated autophosphorylation of erbB2 in MDA-MB 453 cells. Quinazoline analogs with 7-alkoxyamine solubilizing groups were potent irreversible inhibitors of the isolated EGFR enzyme, with IC₅₀[app] values from 2 to 4 nM, and potently inhibited both EGFR and erbB2 autophosphorylation in cells. 7-Alkylamino- and 7-alkoxyaminopyrido[3,2-d]pyrimidines were also irreversible inhibitors with equal or superior potency against the isolated enzyme but were less effective in the cellular autophosphorylation assays. Both quinazoline- and pyrido[3,2-d]pyrimidine-6-acrylamides bound at the ATP site alkylating cysteine 773, as shown by electrospray ionization mass spectrometry, and had similar rates of absorptive and secretory transport in Caco-2 cells. A comparison of two 7-propoxymorpholide analogs showed that the pyrido[3,2-d]pyrimidine-6-acrylamide had greater amide instability and higher acrylamide reactivity, being converted to glutathione adducts in cells more rapidly than the corresponding quinazoline. This difference may contribute to the obsd. lower cellular potency of the pyrido[3,2-d]pyrimidine-6-acrylamides. Selected compds. showed high in vivo activity against A431 xenografts on oral dosing, with the quinazolines being superior to the pyrido[3,2-d]pyrimidines. Overall, the quinazolines proved superior to previous analogs in terms of aq. solv., potency, and in vivo antitumor activity, and one example (CI 1033) has been selected for clin. evaluation.

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 24 CAPLUS COPYRIGHT 2003 ACS
 AN 1998:323483 CAPLUS
 DN 129:119500
 TI Inhibitors of the epidermal growth factor receptor protein tyrosine kinase. A quantitative structure-activity relationship analysis

AU Singh, P.; Kumar, R.
 CS Department Chemistry, S. K. Government College, Sikar, 332001, India
 SO Journal of Enzyme Inhibition (1998), 13(2), 125-134
 CODEN: ENINEG; ISSN: 8755-5093
 PB Harwood Academic Publishers
 DT Journal
 LA English
 IT 171745-06-5
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
 (quant. structure-activity relationship of inhibitors of the epidermal growth factor receptor protein tyrosine kinase)
 RN 171745-06-5 CAPLUS
 CN 4,6-Quinazolinediamine, N4-(3-bromophenyl)-7-methoxy- (9CI) (CA INDEX NAME)



AB Hansch and Free-Wilson analyses are described on a data set, 4-anilinoquinazolines [the analogs of 4-(3-bromo-anilino)-6,7-dimethoxy quinazoline: PD 153035], as inhibitors of the epidermal growth factor receptor protein tyrosine kinase. These analyses have helped to ascertain the role of different substituents in explaining the obsd. inhibitory activities. From both approaches, it is concluded that the combined electron-donating nature of R1- and R2-substitutions of the quinazoline ring and the electron-withdrawing nature of the X-substitution of the anilino-ring are beneficial for increasing the inhibition activity of a compd. Further, the sym. alkoxy substituents present at the R1- and R2-positions are also engaged in a steric interaction which was detd. quant. through the parabolic relationship between the activity and combined molar refraction parameter, .SIGMA.MR of the substituents.

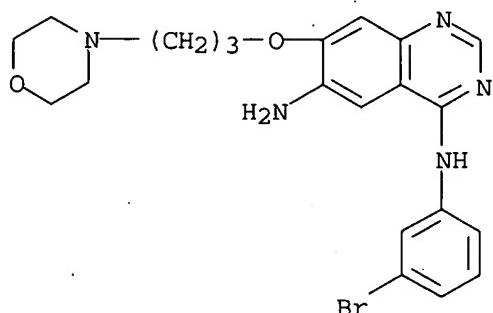
L4 ANSWER 18 OF 24 CAPLUS COPYRIGHT 2003 ACS
 AN 1997:696745 CAPLUS
 DN 128:3695
 TI Preparation of N-quinazolinylacrylamides and analogs as tyrosine kinase inhibitors
 IN Bridges, Alexander James; Denny, William Alexander; Dobrusin, Ellen Myra; Doherty, Annette Marian; Fry, David W.; McNamara, Dennis Joseph; Showalter, Howard Daniel Hollis; Smaill, Jeffrey B.; Zhou, Hairong; et al.
 PA Warner-Lambert Company, USA; Bridges, Alexander James; Denny, William Alexander; Dobrusin, Ellen Myra; Doherty, Annette Marian; Fry, David W.; McNamara, Dennis Joseph; Showalter, Howard Daniel Hollis; Smaill, Jeffrey B.; Zhou, Hairong
 SO PCT Int. Appl., 193 pp.
 CODEN: PIXXD2

DT Patent
 LA English
 FAN.CNT 1

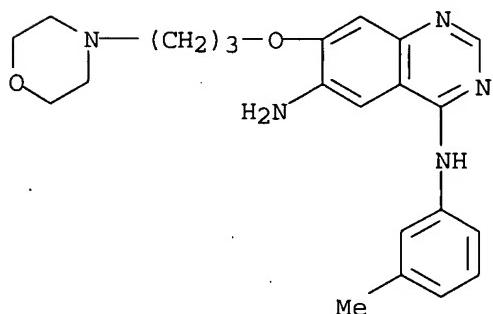
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9738983	A1	19971023	WO 1997-US5778	19970408
	W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GH, HU, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA	2249446	AA	19971023	US 1996-15351P P	19960412
AU	9724463	A1	19971107	CA 1997-2249446	19970408
AU	725533	B2	20001012	US 1996-15351P P	19960412
EP	892789	A1	19990127	AU 1997-24463	19970408
EP	892789	B1	20020227	US 1996-15351P P	19960412
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI			WO 1997-US5778 W	19970408
CN	1218456	A	19990602	EP 1997-920213	19970408
BR	9708640	A	19990803	US 1996-15351P P	19960412
JP	2000508657	T2	20000711	BR 1997-8640	19970408
JP	3370340	B2	20030127	US 1996-15351P P	19960412
AT	213730	E	20020315	WO 1997-US5778 W	19970408
ES	2174250	T3	20021101	AT 1997-920213	19970408
ZA	9703060	A	19971104	US 1996-15351P P	19960412
BG	63160	B1	20010531	WO 1997-US5778 W	19970408
NO	9804718	A	19981209	ZA 1997-3060	19970410
KR	2000005364	A	20000125	US 1996-15351P P	19960412
US	6344459	B1	20020205	BG 1998-102811	19981001
OS	MARPAT 128:3695			US 1996-15351P P	19960412
IT	198961-78-3P	198961-80-7P	198961-82-9P	US 1996-15351P P	19960412
	198961-84-1P	198961-86-3P	198961-87-4P	WO 1997-US5778 W	19970408
	RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)			KR 1998-708086	19981010
	(prep. of N-quinazolinylacrylamides and analogs as tyrosine kinase			US 1996-15351P P	19960412
				US 1999-155501	19990608
				US 1996-15351P P	19960412
				WO 1997-US5778 W	19970408

inhibitors)

RN 198961-78-3 CAPLUS

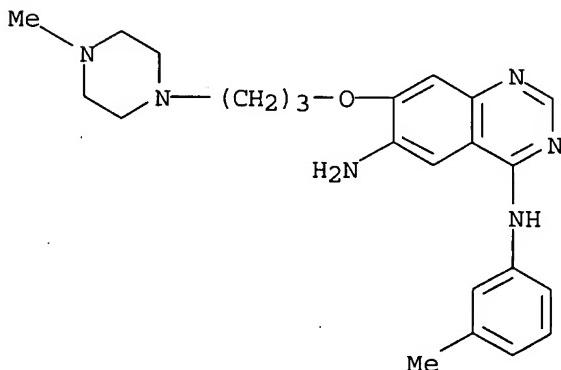
CN 4,6-Quinazolinediamine, N4-(3-bromophenyl)-7-[3-(4-morpholinyl)propoxy] -
(9CI) (CA INDEX NAME)

RN 198961-80-7 CAPLUS

CN 4,6-Quinazolinediamine, N4-(3-methylphenyl)-7-[3-(4-morpholinyl)propoxy] -
(9CI) (CA INDEX NAME)

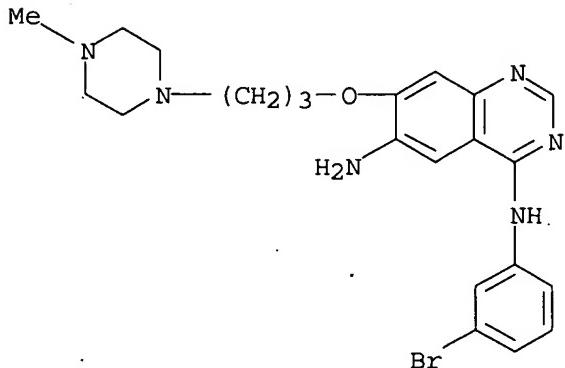
RN 198961-82-9 CAPLUS

CN 4,6-Quinazolinediamine, N4-(3-methylphenyl)-7-[3-(4-methyl-1-piperazinyl)propoxy] - (9CI) (CA INDEX NAME)



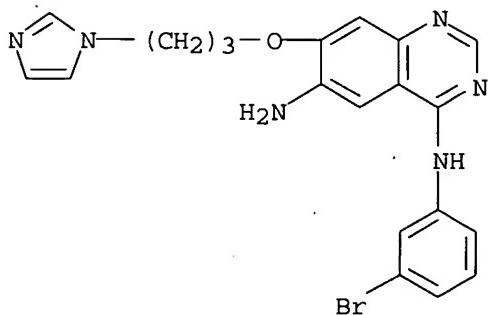
RN 198961-84-1 CAPLUS

CN 4,6-Quinazolinediamine, N4- (3-bromophenyl) -7- [3- (4-methyl-1-piperazinyl)propoxy] - (9CI) (CA INDEX NAME)



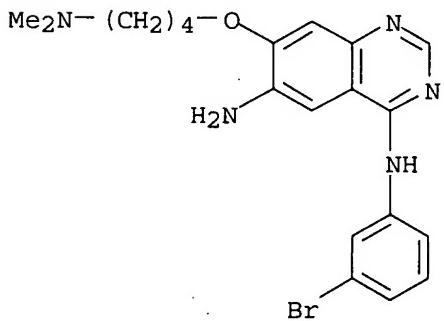
RN 198961-86-3 CAPLUS

CN 4,6-Quinazolinediamine, N4- (3-bromophenyl) -7- [3- (1H-imidazol-1-yl)propoxy] - (9CI) (CA INDEX NAME)

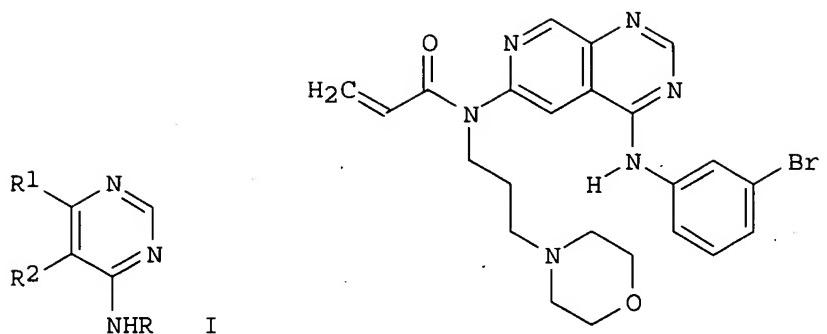


RN 198961-87-4 CAPLUS

CN 4,6-Quinazolinediamine, N4- (3-bromophenyl) -7- [4- (dimethylamino)butoxy] - (9CI) (CA INDEX NAME)



GI



AB Title compds. [I; R = (CHR₆)pR₉; R₁R₂ = CH:CR₇CR₈:CH, CH:CR₇CR₈:N, CH:CR₇N:CH, etc.; R₆ = H or alkyl; 1 of R₇, R₈ = Z₁Z₂R₁₀ and the other = OR₄, SR₄, NHR₃; R₃, R₄ = (un)substituted alkyl, heterocyclalkyl, etc.; R₉ = (un)substituted Ph; R₁₀ = CR₁₁:CHR₅, C.tplbond.CR₅, CR₁₁:C:CHR₅; R₅ = H, halo, alkyl, Ph, etc.; R₁₁ = H, halo, alkyl; Z₁ = bond, O, (alkyl)imino, CH₂, etc.; Z₂ = CO, SO, P(O)(OH), etc.; p = 0 or 1] were prep'd. Thus, I (R = C₆H₄Br-3, R₁R₂ = CH:NCR₈:CH, R₈ = F) was condensed with 3-morpholinopropanamine and the product acylated by CH₂:CHCOCl to give title compd. II. Data for biol. activity of I were given.

L4 ANSWER 19 OF 24 CAPLUS COPYRIGHT 2003 ACS

AN 1996:756470 CAPLUS

DN 126:18889

TI Preparation of 6-(2-methoxyethylamino)-7-methoxy-4-(3'-methylanilino)quinazoline cell proliferation inhibitor

IN Barker, Andrew John

PA Zeneca Limited, UK

SO PCT Int. Appl., 21 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9633981	A1	19961031	WO 1996-GB962	19960423
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN			GB 1995-8535	A 19950427
AU 9653434		A1	19961118	AU 1996-53434	19960423
				GB 1995-8535	A 19950427
				WO 1996-GB962	W 19960423
EP 823901		A1	19980218	EP 1996-910135	19960423
EP 823901		B1	20001018		
	R: CH, DE, FR, GB, IT, LI			GB 1995-8535	A 19950427
JP 11504034		T2	19990406	WO 1996-GB962	W 19960423
				JP 1996-532253	19960423

US 5952333	A 19990914	GB 1995-8535 A 19950427
		WO 1996-GB962 W 19960423
		US 1997-930044 19970926
		GB 1995-8535 A 19950427
		WO 1996-GB962 W 19960423

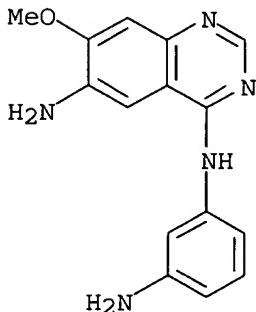
OS MARPAT 126:18889

IT 184473-34-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (prepn. of 6-(2-methoxyethylamino)-7-methoxy-4-(3'-methylanilino)quinazoline cell proliferation inhibitor)

RN 184473-34-5 CAPLUS

CN 4,6-Quinazolinediamine, N4-(3-aminophenyl)-7-methoxy- (9CI) (CA INDEX NAME)



AB 6-(2-Methoxyethylamino)-7-methoxy-4-(3'-methylanilino)quinazoline, useful as a cell-inhibiting tyrosine kinase receptor inhibitor for the treatment of proliferative diseases such as cancer (no data), prep'd. by the reaction of 2-methoxyacetaldehyde di-Me acetal and 6-amino-7-methoxy-4-(3'methylanilino)quinazoline in the presence of NaBH4, demonstrated a IC50 of 0.01 .mu.M against the enzyme EGF receptor tyrosine kinase.

L4 ANSWER 20 OF 24 CAPLUS COPYRIGHT 2003 ACS

AN 1996:483485 CAPLUS

DN 125:142741

TI Prepn. of N-phenyl-4-quinazolinamines for the treatment of proliferative diseases

IN Brown, Dearg Sutherland; Morris, Jeffrey James; Thomas, Andrew Peter

PA Zeneca Limited, UK

SO PCT Int. Appl., 120 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9615118	A1	19960523	WO 1995-GB2606	19951108
	W:	AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK			
	RW:	KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			

			GB 1994-22866	19941112
			GB 1995-7308	19950407
CA 2200871	AA	19960523	CA 1995-2200871	19951108
			GB 1994-22866	19941112
			GB 1995-7308	19950407
AU 9538130	A1	19960606	AU 1995-38130	19951108
AU 703328	B2	19990325		
			GB 1994-22866	19941112
			GB 1995-7308	19950407
			WO 1995-GB2606	19951108
EP 790986	A1	19970827	EP 1995-936044	19951108
EP 790986	B1	19990120		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
			GB 1994-22866	19941112
			GB 1995-7308	19950407
			WO 1995-GB2606	19951108
JP 10508616	T2	19980825	JP 1995-515816	19951108
			GB 1994-22866	19941112
			GB 1995-7308	19950407
			WO 1995-GB2606	19951108
AT 175962	E	19990215	AT 1995-936044	19951108
			GB 1994-22866	19941112
			GB 1995-7308	19950407
ES 2128092	T3	19990501	ES 1995-936044	19951108
			GB 1994-22866	19941112
			GB 1995-7308	19950407
ZA 9509572	A	19960513	ZA 1995-9572	19951110
			GB 1994-22866	19941112
FI 9701970	A	19970507	FI 1997-1970	19970507
			GB 1994-22866	19941112
			GB 1995-7308	19950407
			WO 1995-GB2606	19951108
NO 9702152	A	19970512	NO 1997-2152	19970509
			GB 1994-22866	19941112
			GB 1995-7308	19950407
			WO 1995-GB2606	19951108
US 5821246	A	19981013	US 1997-836362	19970521
			GB 1994-22866	19941112
			GB 1995-7308	19950407
			WO 1995-GB2606	19951108

OS MARPAT 125:142741

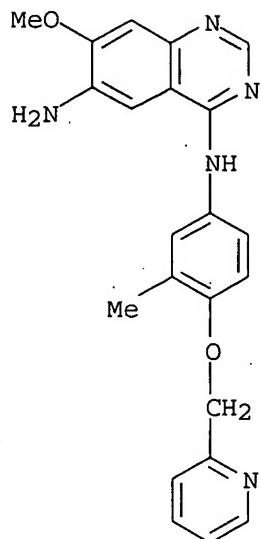
IT 179688-72-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)

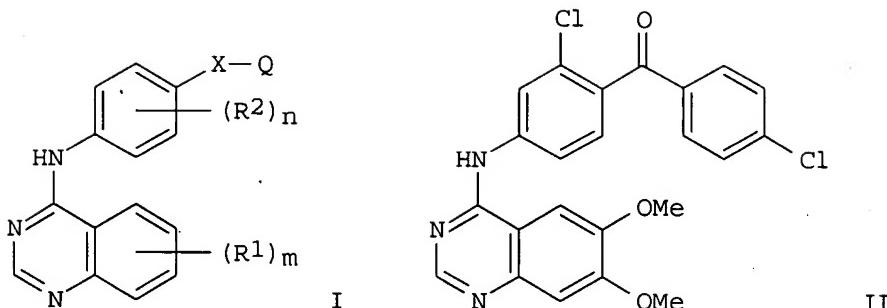
(prepn. of N-phenylquinazolinamines as tyrosine kinase inhibitors)

RN 179688-72-3 CAPLUS

CN 4,6-Quinazolinediamine, 7-methoxy-N4-[3-methyl-4-(2-pyridinylmethoxy)phenyl]- (9CI) (CA INDEX NAME)



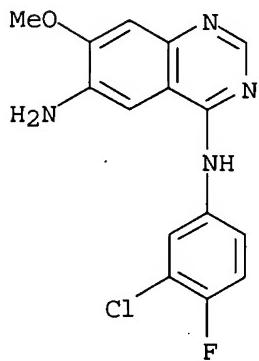
GI



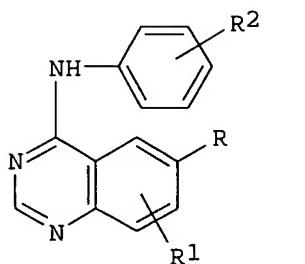
AB The title compds. I ($m = 1-3$; $R1 = \text{halo, hydroxy, amino, ureido, etc.}; n = 0-3$; $R2 = \text{halo, trifluoromethyl, hydroxy, amino, nitri, cyano, alkyl}; X = \text{carbonyl, methine, O,S, etc.}$) were disclosed. I were claimed for the use as receptor tyrosine kinase inhibitors and for treatment of proliferative disease such as cancer. An example compd. is the chlorophenyl [(quinazolinyl)amino]phenyl methanone II.

L4 ANSWER 21 OF 24 CAPLUS COPYRIGHT 2003 ACS
 AN 1996:476843 CAPLUS
 DN 125:142761
 TI Quinazoline derivatives
 IN Barker, Andrew John
 PA Zeneca Limited, UK
 SO PCT Int. Appl., 45 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9616960	A1	19960606	WO 1995-GB2768	19951128
	W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU	9539330	A1	19960619	GB 1994-24233	19941130
				AU 1995-39330	19951128
				GB 1994-24233	19941130
				WO 1995-GB2768	19951128
EP	794953	A1	19970917	EP 1995-937126	19951128
EP	794953	B1	19990506		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
				GB 1994-24233	19941130
				WO 1995-GB2768	19951128
JP	10509972	T2	19980929	JP 1995-518417	19951128
				GB 1994-24233	19941130
				WO 1995-GB2768	19951128
AT	179708	E	19990515	AT 1995-937126	19951128
				GB 1994-24233	19941130
US	5955464	A	19990921	US 1997-860088	19970522
				GB 1994-24233	19941130
				WO 1995-GB2768	19951128
OS	MARPAT 125:142761				
IT	179552-75-1P				
	RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)				
	(prepn. of tyrosine kinase inhibiting imidazolylquinazolines)				
RN	179552-75-1 CAPLUS				
CN	4,6-Quinazolinediamine, N4-(3-chloro-4-fluorophenyl)-7-methoxy- (9CI) (CA INDEX NAME)				

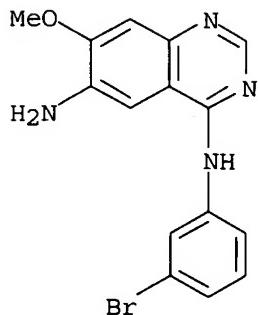


GI



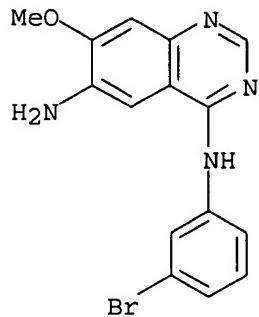
AB The invention concerns quinazoline derivs. I ($m = 1, 2$; $R1 = H, \text{halo, alkyl, alkoxy}$; $n = 1-3$; $R2 = H, OH, \text{halo, alkyl}$; $R = 5-$ or 9 -membered nitrogen-linked heteroaryl moiety contg. up to four nitrogen heteroatoms, or $R =$ a $5-, 6-, 9-$ or 10 -membered nitrogen-linked unsatd. heterocyclic moiety contg. up to three nitrogen heteroatoms which bears one or two substituents selected from oxo and thioxo) and the use of the receptor tyrosine kinase inhibitory properties of the compds. in the treatment of proliferative diseases such as cancer. Among the approx. 15 title compds. prep'd., $4-(3\text{-methylanilino})-$, $4-(3\text{-chloro-4-fluoroanilino})-$, $4-(4\text{-benzoyl-3-chloroanilino})-$, and $4-[3\text{-methyl-4-(2-pyridylmethoxy)anilino}-6-(1-imidazolyl)quinazolines$ were claimed.

L4 ANSWER 22 OF 24 CAPLUS COPYRIGHT 2003 ACS
 AN 1996:312235 CAPLUS
 DN 125:25623
 TI Structure-activity relationships for 4-anilinoquinazolines as potent inhibitors at the ATP binding site of the epidermal growth factor receptor *in vitro*
 AU Denny, William A.; Newcastle, Gordon W.; Bridges, Alexander J.; Fry, David W.; Kraker, Alan J.
 CS Cancer Research Lab., Univ. Auckland School Medicine, Auckland, 92019, N. Z.
 SO Clinical and Experimental Pharmacology and Physiology (1996), 23(5), 424-427
 CODEN: CEXPB9; ISSN: 0305-1870
 PB Blackwell
 DT Journal
 LA English
 IT 171745-06-5
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (anilinoquinazolines as potent inhibitors at ATP binding site of epidermal growth factor receptor)
 RN 171745-06-5 CAPLUS
 CN 4,6-Quinazolinediamine, N4-(3-bromophenyl)-7-methoxy- (9CI) (CA INDEX NAME)



AB Structure-activity relationships are described for the inhibition of the tyrosine kinase activity (phosphorylation of a fragment of phospholipase C_{g1}) of the epidermal growth factor receptor (EGFR) by 4-anilinoquinazolines. These compds. are competitive inhibitors at the ATP binding site. The preferred side chain is anilino-, substituted at the 3-position with small lipophilic groups. The quinazoline moiety is absolutely required for activity, but substituents on the quinazoline greatly modulate potency, with electron-donating groups favored. The most potent analog, the 6,7-dimethoxy deriv., has an IC₅₀ of 29 pmol/L and a very high selectivity for the EGFR over other tyrosine kinase enzymes. The present study shows that it is possible to identify small mols. that are very potent, yet highly selective, inhibitors of a single component of the growth signal transduction pathway in cells.

L4 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2003 ACS
 AN 1995:983167 CAPLUS
 DN 124:21051
TI Tyrosine kinase inhibitors: unusually steep structure-activity relationship for analogs of 4-(3-bromoanilino)-6,7-dimethoxyquinazoline (PD 153035), a potent inhibitor of the epidermal growth factor receptor
AU Bridges, Alexander J.; Zhou, Hairong; Cody, Donna R.; Newcastle, Gordon W.; McMichael, Amy; Showalter, H. D. Hollis; Fry, David W.; Kraker, Alan J.; Denny, William A.
CS Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, MI, 48106-1047, USA
SO Journal of Medicinal Chemistry (1996), 39(1), 267-76
 CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
IT 171745-06-5
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (epidermal growth factor receptor tyrosine kinase inhibitors:
 structure-activity relations for analogs of
 (bromoanilino)dimethoxyquinazoline (PD 153035))
RN 171745-06-5 CAPLUS
CN 4,6-Quinazolinediamine, N4-(3-bromophenyl)-7-methoxy- (9CI) (CA INDEX NAME)



AB 4-(3-Bromoanilino)-6,7-dimethoxyquinazoline (PD 153035) is a very potent inhibitor (IC_{50} 0.025 nM) of the tyrosine kinase activity of the EGF receptor, binding competitively at the ATP site. Structure-activity relations for close analogs of PD 153035 are very steep. Some derivs. have IC_{50} \approx 80-fold better than predicted from simple additive binding energies, yet analogs possessing combinations of similar Ph and quinazoline substituents do not show this supra-additive effect. Some substituents which are mildly deactivating by themselves can be strongly activating when used in the correct combinations; therefore, certain substituted analogs may induce a change in conformation of the receptor when they bind. There is some bulk tolerance for substitution in the 6- and 7-positions of the quinazoline, so that PD 153035 is not the optimal inhibitor for the induced conformation. 4-(3-Bromoanilino)-6,7-diethoxyquinazoline shows an IC_{50} of 0.006 nM, making it the most potent inhibitor of the tyrosine kinase activity of the EGF receptor yet reported.

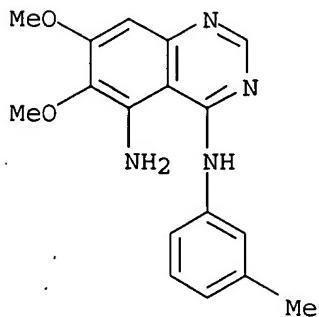
L4 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2003 ACS
 AN 1994:217715 CAPLUS
 DN 120:217715
 TI Quinazoline tyrosine kinase-inhibiting anticancer agents
 IN Barker, Andrew J.
 PA Zeneca Ltd., UK
 SO Can. Pat. Appl., 99 pp.
 CODEN: CPXXEB

DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CA 2086968	AA	19930721	CA 1993-2086968	19930108
	CA 2086968	C	19980623	GB 1992-1095	A 19920120
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				GB 1992-23735	A 19921112
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				GB 1992-1095	A 19920120
	AU 9331010	A1	19930722	AU 1993-31010	19930104
	AU 661533	B2	19950727	GB 1992-1095	A 19920120
				GB 1992-13572	A 19920626
				GB 1992-23735	A 19921112
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				GB 1992-1095	A 19920120
				GB 1992-13572	A 19920626

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EP 566226	B1	19951108	EP 1993-300270 19930115
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GB 1992-1095 A 19920120			
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SK 281551	B6	20010510	SK 1993-16 19930119
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GB 1992-23735 A 19921112			
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OS	MARPAT 120:217715		
IT	153437-12-8P		
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)			
(prepn. of, as intermediate in prepn. of quinazoline tyrosine kinase-inhibiting anticancer agents)			
RN	153437-12-8 CAPLUS		
CN	4,5-Quinazolinediamine, 6,7-dimethoxy-N4-(3-methylphenyl)- (9CI) (CA)		

(INDEX NAME)



IT 153437-18-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of, as tyrosine kinase-inhibiting anticancer agent)

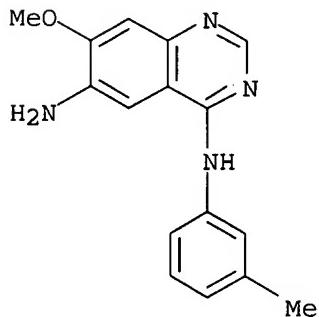
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CN 4,6-Quinazolinediamine, 7-methoxy-N4-(3-methylphenyl)-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

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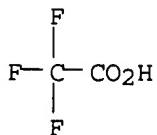
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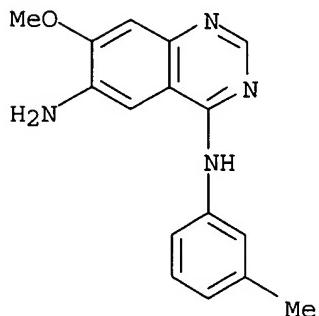


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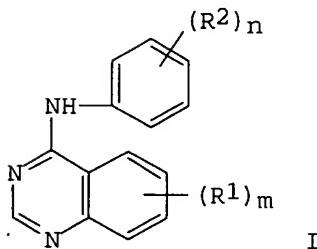
RL: RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
 (tyrosine kinase-inhibiting anticancer agent)

RN 153437-17-3 CAPLUS

CN 4,6-Quinazolininediamine, 7-methoxy-N4-(3-methylphenyl)- (9CI) (CA INDEX
 NAME)



GI



AB The title compds. I [R1 = HO, (un)substituted amino, carboxy, carbamoyl, ureido, etc.; R2 = H, HO, halogen, CF₃, NH₂, NO₂, CN, (un)substituted C₁₋₄ alkyl, etc.; m = 1-3; n = 1, 2], useful as tyrosine kinase-inhibiting anticancer agents (no data), are prep'd. and I-contg. formulations presented. Thus, 4-chloro-6,7-dimethoxyquinazoline was condensed with 3-MeC₆H₄NH₂, producing 6,7-dimethoxy-4-(3'-methylanilino)quinazoline hydrochloride, m.p. 248-249.degree..

=> s 14 and Tyrosine kinase
 L5 18 L4 AND TYROSINE KINASE

=> d his

(FILE 'HOME' ENTERED AT 14:38:38 ON 01 JUL 2003)

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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION	
CA SUBSCRIBER PRICE	-15.62	-15.62	

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